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Original article

Antimicrobial and cancer cell growth inhibitory activities of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane in vitro

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Abstract

The in vitro activity of the steroidal amide 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane against 179 Gram-positive clinical isolates was examined. The minimum bactericidal concentration (MBC)/MIC ratios were ≤2 for 73% of methicillin-resistant *Staphylococcus aureus*, 59% of vancomycin-resistant *Enterococcus* spp. and 88% of penicillin-resistant *Streptococcus pneumoniae*. The androstane derivative was bactericidal for a variety of other Gram-positive genera, including *Nocardia*, *Corynebacterium* and *Listeria*. Variation in MICs is pH 6–8 media was slight. The frequency of occurrence of bacterial spontaneous mutations to resistance ranged from 10^{-8} to 10^{-9}. Kill curve analysis confirmed the bactericidal nature of the steroidal amide, and demonstrated that killing was time dependent but not concentration dependent for all organisms. The ability of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane to inhibit human cancer cell growth was also evaluated. The concentration required to inhibit 50% of cell growth (GI_{50}) was <2.5 mg/l for all cell lines examined. In single-dose murine toxicity evaluations, the androstane derivative was non-toxic at doses up to 400 mg/kg.

Keywords: Antibacterial susceptibility; Steroidal amide

1. Introduction

An alarming increase in resistance of Gram-positive bacteria to available antimicrobials is developing, limiting the options for effective treatment. Several of the more important resistance problems include vancomycin resistance in enterococci, penicillin resistance in streptococci and methicillin resistance in staphylococci [1,2]. A major research emphasis to counter this growing problem is the development of antimicrobials structurally unrelated to existing antimicrobials.

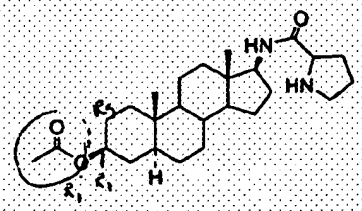

Fig. 1. Structure of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane.

Our synthesis of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane was reported in 1967 [3]. More than 30 years later, its effects on cancer and bacterial cell growth were investigated and the results reported here. The steroidal amide is a promising new antitumour antimicrobial, with activity against all human cancer cell lines and antibiotic-resistant Gram-positive bacteria examined.

2. Methods

2.1. 3β-Acetoxy-17β-(L-prolyl)amino-5α-androstane

The androstane derivative (Fig. 1) was synthesized in our laboratory as previously described [3], stored desic-

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Table 1
Inhibition of murine P388 lymphocytic leukaemia and human cancer cell line growth by 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane

Cell line	GI_{50}[a] (mg/l)
P388	2.14
Pancreas BXPC-3	1.9
Ovarian OVCAR-3	2.0
CNS SF-295	1.9
Lung-NSC NCI-H460	2.1
Colon KM20L2	2.6
Prostate DU-145	1.9

[a] GI_{50}, Inhibition of 50% cell growth.

Table 2
Antimicrobial activities of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane for reference strains in the disk diffusion assay

Organism	ATCC (Presque Isle) number	MIC (μg/disk)
Staphylococcus aureus	29 213	12.5–25
Staphylococcus epidermis	(4653)	6.25–12.5
Enterococcus faecalis	29 212	25–50
Streptococcus pneumoniae	6303	50–100
Micrococcus luteus	(456)	1.56–3.12
Bacillus subtilis	(620)	3.12–6.25
Stenotrophomonas maltophila	13 637	>100
Pseudomonas aeruginosa	(99)	>100
Escherichia coli	25 922	>100
Neisseria gonorrhoeae	49 226	>100
Enterobacter cloacae	13 047	>100
Klebsiella pneumoniae	(344)	>100
Proteus vulgaris	(365)	>100
Candida albicans	90 028	>100
Cryptococcus neoformans	90 112	>100

cated and, prior to each assay, suspended in a small volume of MeOH and diluted in the appropriate broth.

2.2. Cancer cell line testing

Inhibition of cancer cell growth was assessed using the National Cancer Institute's standard Sulforhodamine B assay as previously described [4]. Briefly, cells in 5% foetal calf serum/RPMI-1640 were inoculated into 96-well plates, incubated for 24 h and 10-fold dilutions of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane added. After a 48 h incubation, plates were fixed with trichloroacetic acid, washed, stained with Sulforhodamine B and read with an automated microtitre plate reader. Growth inhibition of 50% (GI_{50} or the drug concentration causing a 50% reduction in the net protein increase in control cells during the drug incubation) was calculated from optical density data with IMMUNOSOFT software. Sulforhodamine B assays were performed once in duplicate.

2.3. Bacterial strains

Non-duplicate clinical isolates and antibiotic resistance information were obtained from the Arizona Department of Health Services. Invasive *Streptococcus pneumoniae* were cultured from sterile sites; their antibiotic resistance profiles had not been determined. Reference strains were obtained from the American Type Culture Collection (Rockville, MD) or Presque Isle Cultures (Presque Isle, PA).

2.4. Disk diffusion susceptibility testing

Disk assays were performed according to National Committee for Clinical Laboratory Standards (NCCLS) [5]. Mueller–Hinton agar supplemented with 5% sheep blood was used for *S. pneumoniae*, gonococcal typing agar for *Neisseria gonorrhoeae* and Mueller–Hinton agar for all other bacteria. Sabouraud dextrose agar was used for yeast strains. The MIC was defined as the lowest drug concentration resulting in a clear zone of growth inhibition.

2.5. Broth macrodilution susceptibility testing

3β-Acetoxy-17β-(L-prolyl)amino-5α-androstane was screened against reference strains and clinical isolates by the NCCLS broth macrodilution assay [6]. Isolated colonies from overnight cultures were suspended and diluted as recommended to yield final inocula of approximately 5×10^5 CFU/ml. Tests were performed in sterile plastic tubes (12 × 75 mm) containing twofold dilutions of the androstane derivative in Mueller–Hinton II (MHII) (cation adjusted) broth containing 3% lysed horse blood (*Streptococcus, Arcanobacterium, Lactobacillus, Gardnerella*) or MHII broth (all other bacteria). One tube was left drug free (but contained an equivalent volume of MeOH) as a turbidity control. Tubes were incubated without agitation at 37°C with 5% CO_2 (*Streptococcus, Arcanobacterium, Lactobacillus, Gardnerella*), at 37°C (*Staphylococcus, Enterococcus*) or at 35°C (*Bacillus, Paenibacillus, Rhodococcus, Gordona, Micrococcus, Listeria, Corynebacterium, Nocardia*). MICs were determined after 24 h for all organisms except *Gardnerella* and *Rhodococcus*, which were read after 48 h, and *Gordona sputi*, which was read at 72 h. The MIC was defined as the lowest concentration of drug that inhibited all visible growth of the test organism (optically clear). Broth macrodilution assays were also performed on three separate days in MHII broth prepared at pH 6, 7 and 8.

2.6. Minimum bactericidal concentrations

Minimum bactericidal concentrations (MBCs) were determined by subculturing 0.1 ml from each tube with no visible growth in the MIC broth macrodilution series onto drug-free plates. The plates were incubated at the appropriate temperature for 24–48 h. The MBC was defined as the lowest drug concentration that resulted in ≥99.9% reduction in the initial inoculum.

2.7. Time-kill studies

Overnight cultures of *Staphylococcus aureus* 29213, *Enterococcus faecalis* 29212 and *S. pneumoniae* 6303 in MHII broth were inoculated into the same medium containing multiples of the broth macrodilution MIC of the steroidal amide, or an equivalent volume of MeOH. Cultures were shaken at 37°C, and aliquots were aseptically removed at various times for dilution plating. Standard errors of the means were calculated from at least two experiments. The detection limit in these experiments was 10 CFU/ml.

2.8. Frequency of spontaneous mutants

Overnight cultures of *S. aureus* 29213, *E. faecalis* 29212, *S. pneumoniae* 6303 and *Bacillus subtilis* 620 were diluted to $OD_{625nm} = 0.08$. Each preparation (0.1

Table 3
Broth macrodilution MICs and MBCs of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane for clinical isolates

Organism (number of strains)	MIC (mg/l)			MBC (mg/l)		
	Range	50%[a]	90%[a]	Range	50%[b]	90%[b]
Methicillin-resistant *S. aureus* (22)	4–8	8	8	8 to >64	16	>64
S. saprophyticus (3)	4–8			8	16	>64
Vancomycin-resistant *Enterococcus* spp. (34)	4–16	8	16	8 to >64		
Vancomycin-resistant *E. faecalis* (2)	8–16			16–64		
Vancomycin-resistant *E. faecium* (2)	8–16			16–64		
Penicillin-resistant *Streptococcus pneumoniae* (35)	8–32	16	16	8 to >64	16	32
Invasive *S. Pneumoniae* (15)	8–16	8	16	8–64	16	16
Group A Streptococci (18)	8–16	8	16	8–32	16	32
Bacillus subtilis (4)	8			8 to >64		
B. cereus (5)	32			>64		
B. circulans (1)	16			>64		
B. licheniformis (1)	32			>64		
Paenibacillus alvei (1)	16			>64		
Rhodococcus spp. (19)	4–64	8	16	8 to >64	16	32
R. equi (3)	4–8			16–32		
Gordona bronchialis (1)	8			8		
G. sputi (1)	8			32		
Listeria monocytogenes (3)	16–32			32–64		
Corynbacterium diphtheriae (3)	4–8			8		
Nocardia asteroides (1)	8			32		
N. farcinica (1)	16			64		
Lactobacillus spp. (1)	16			32		
Arcanobacterium haemolyticum (1)	16			32		
Gardnerella vaginalis (2)	4			8		

[a] 50% and 90%, MICs at which 50 and 90% of the strains, respectively, are inhibited.
[b] 50% and 90%, MBCs at which 50 and 90% of the strains, respectively, are killed.

Table 4
Broth macrodilution MICs and MBCs of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane for reference strains

Organism	ATCC (Presque Isle) number	MIC (mg/l)	MBC (mg/l)
Staphylococcus aureus	29213	4	64
S. epidermidis	(4653)	8	32
Enterococcus faecalis	29212	16	32
Streptococcus pneumoniae	6303	16	16
Bacillus subtilis	(620)	4	4
Micrococcus luteus	(456)	8	64
Corynebacterium hoagi	7005	8	32

Table 5
Effect of pH on broth macrodilution MICs (range of three determinations) of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane for reference strains and clinical isolates

Organism	pH	MIC range (mg/l)
Methicillin-resistant *S. Aureus*[a]	6	16
	7	8
	8	4
S. aureus ATCC 29213	6	8–16
	7	8
	8	4
Vanomycin-resistant *E. Faeculis*[a]	6	32
	7	8
	8	4–8
E. faecalis ATCC 29212	6	32
	7	8–16
	8	4–8
Bacillus subtilis Presque Isle 620	6	8
	7	4–8
	8	4–8
Listeria monocytogenes[a]	6	32
	7	16–32
	8	16
Corynebacterium diphtheriae[a]	6	16
	7	4–8
	8	2–4

[a] Clinical isolate.

ml) was spread onto agar plates containing four or eight times the broth macrodilution MIC of the androstane derivative. The starting inoculum for each organism was also diluted and plated onto drug-free plates for determination of CFU/ml. After 24 h incubation at the appropriate temperature, the number of bacterial colonies on drug-supplemented agar was counted. The frequency of occurrence of spontaneous mutants was calculated by dividing the number of colonies on drug-containing plates by the number of colonies in the inoculum. When no colonies were visualized on drug-containing plates, the calculation was (<)1 colony divided by the number of colonies in the inoculum.

2.9. Mouse toxicity evaluation

Female CD-1 mice were obtained from Charles River Laboratories at approximately 3 weeks of age and assigned randomly into test groups. 3β-Acetoxy-17β-(L-prolyl)amino-5α-androstane was dissolved in tissue cul-

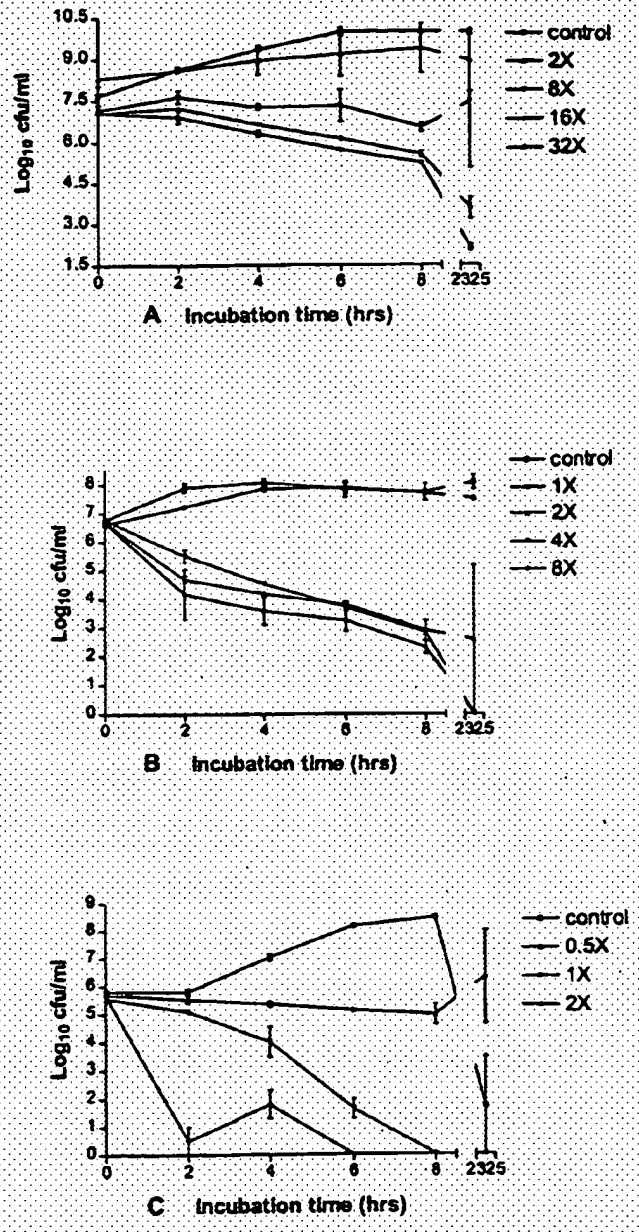

Fig. 2. Kill curves for *S. aureus* 29213 (A), *E. faecalis* 29212 (B) and *S. pneumoniae* 6303 (C) with indicated multiples of steroidal amide MIC. Results are the means ± the standard errors of the means of at least two experiments.

Table 6
Frequency of occurrence of spontaneous mutants resistant to 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane

Organism	ATCC (Presque Isle) number	Frequency at 4× MIC	Frequency at 8× MIC
Staphylococcus aureus	29213	1.2×10^{-6}	$<6 \times 10^{-9}$
Enterococcus faecalis	29213	8.9×10^{-7}	$<1 \times 10^{-8}$
Streptococcus pneumoniae	6303	$<3.3 \times 10^{-6}$	$<3.3 \times 10^{-6}$
Bacillus subtilis	(620)	$<2.2 \times 10^{-7}$	$<2.2 \times 10^{-7}$

ture grade dimethyl sulfoxide and diluted in sterile 0.9% saline prior to injection. Mice given a single injection (intraperitoneally (i.p.)) of drug at 50, 100, 200 or 400 mg were held for observation a minimum of 5 days prior to necropsy. Groups of mice (three per group) given twice daily injections (i.p.) of diluent or compound at 12.5, 25, or 37.5 mg/kg/dose were held at least 48 h following the final dosing for observation. Mice were weighed daily and observed for clinical signs.

3. Results and discussion

The biological activity of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane was initially evaluated against a selection of cancer cell lines (Table 1). Subsequently, results with a wide spectrum of microbes in the disk diffusion assay suggested that this steroidal amide was specific for Gram-positive bacteria (Table 2). Well-known antitumour agents with antibacterial activity include the mitomycins, auramycins and daunomycin [7]. In broth macrodilution assays, 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane inhibited the growth of all Gram-positive bacteria tested, including those resistant to methicillin, vancomycin and penicillin (Tables 3 and 4). MBC/MIC ratios were ≤ 2 for 73% of methicillin-resistant *S. aureus*, 59% of vancomycin-resistant *Enterococcus* spp., 88% of penicillin-resistant *S. pneumoniae*, 93% of invasive *S. pneumoniae*, 89% of Group A *Streptococcus* and 58% of *Rhodococcus* spp., consistent with a bactericidal mechanism of action. Given that the majority of bacterial pathogens isolated from cancer patients are Gram-positive [8], the dual biological activities of this compound are noteworthy.

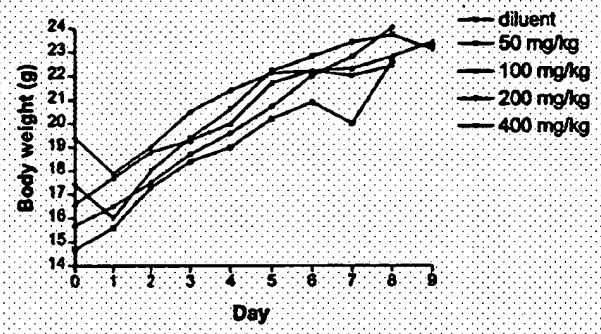

Fig. 3. Body weight over time of mice given a single injection of diluent or steroidal amide at indicated concentrations.

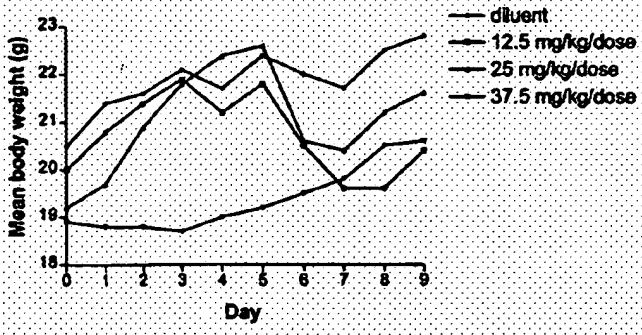

Fig. 4. Mean body weight (three mice per group) of mice given twice daily injections of diluent or steroidal amide at indicated concentrations.

When broth macrodilution assays were performed at pH 6, 7 and 8 on three separate days, MICs were usually within two, 2-fold dilutions (Table 5). The frequency of occurrence of spontaneous mutants resistant to 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane is given in Table 6. Colonies growing on drug-containing agar plates were considered resistant. There were no survivors on plates containing eight times the MIC.

Fig. 2 summarizes the time-kill curves for 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane with *S. aureus* 29213 (Fig. 2A), *E. faecalis* 29212 (Fig. 2B) and *S. pneumoniae* 6303 (Fig. 2C). Killing was time-dependent for *S. aureus*, *E. faecalis* and *S. pneumoniae*, and concentration-dependent for *S. pneumoniae*. For *S. aureus*, time to 99.9% kill was between 8 and 24 h at 16 and 32 times the MIC. For *E. faecalis*, time to 99.9% kill was 8 h at two and four times the MIC, and 4 h at eight times the MIC. For *S. pneumoniae*, time to 99.9% kill was 6 h at the MIC and 2 h at twice the MIC. The number of survivors in cultures of *S. aureus*, *E. faecalis* and *S. pneumoniae* treated with intermediate doses for 24 h varied greatly (note large standard errors at $t = 24$ h for *S. aureus* treated with eight times the MIC, *E. faecalis* treated with twice the MIC and *S. pneumoniae* treated with one-half the MIC). After 24 h, there were no survivors in *E. faecalis* cultures treated with four or eight times the MIC, and *S. pneumoniae* cultures treated with one and two times the MIC.

Individual body weights of mice given a single injection of diluent or 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane are shown in Fig. 3. There were no apparent differences in weight gain in the five groups. All mice remained clinically normal throughout the observation period and all organs appeared grossly normal at necropsy.

Mean body weights of mice given twice-daily injections of diluent or drug are shown in Fig. 4. Mice in the intermediate dose group (25 mg/kg/dose) gained slightly more weight than controls after the 9-day period, for a total of 450 mg/kg. By day 4, mice in the high dose group (37.5 mg/kg/dose) had reduced weight gains and exhibited signs of clinical toxicity. Dosing was discontinued in this group, and weight gains subsequently observed. The diluent, 12.5 and 25 mg/kg/dose groups remained clinically normal throughout the observation period. Future studies will include evaluation of 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane in systemic and non-systemic murine models of Gram-positive infection.

In summary, 3β-acetoxy-17β-(L-prolyl)amino-5α-androstane exhibits properties in vitro which make it an attractive candidate for development as a Gram-positive antimicrobial. We are currently synthesizing derivatives that may be useful for systemic Gram-positive infections in immunosuppressed individuals, including cancer patients.

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lent multicenter data on factors that identify patients at risk for development of cardiogenic shock.
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Webb JG, Carere RG, Hilton JD, et al: Usefulness of coronary stenting for cardiogenic shock. Am J Cardiol 79:81–84, 1997. *Coronary stents can improve flow and reduce recurrent ischemia in cardiogenic shock.*

96 SHOCK SYNDROMES RELATED TO SEPSIS

Joseph E. Parrillo

Sepsis refers to the systemic response to serious infection. Patients with sepsis usually manifest fever, tachycardia, tachypnea, leukocytosis, and a localized site of infection. Microbiologic cultures from blood or the infection site are frequently, though not invariably, positive. When this syndrome results in hypotension or multiple organ system failure, the condition is called *septic shock*.

INCIDENCE AND EPIDEMIOLOGY

The incidence of sepsis and septic shock has been increasing since the 1930s, and all recent evidence suggests that this rise will continue. The reasons for this increasing incidence are many: increased use of invasive devices such as intravascular catheters; widespread use of cytotoxic and immunosuppressive drug therapies for cancer and transplantation; increased lifespan of patients with cancer and diabetes, who are prone to develop sepsis; and increase in infections due to antibiotic-resistant organisms. Septic shock is the most common cause of death in intensive care units, and it is the 13th most common cause of death in the United States. The precise incidence of the disease is not known because it is not reportable; however, a reasonable annual estimate for the United States is 400,000 bouts of sepsis, 200,000 cases of septic shock, and 100,000 deaths from this disease.

ETIOLOGY

Gram-negative and gram-positive organisms as well as fungi can cause sepsis and septic shock. Certain viruses and rickettsiae probably can produce a similar syndrome. Compared with gram-positive organisms, gram-negative bacteria are somewhat more likely to produce septic shock. Culture-positive gram-negative bacteremia produces shock in approximately 50% of infections, whereas gram-positive bacteremia produces shock in about 25% of infections.

Any site of infection can result in sepsis or septic shock. Frequent causes of sepsis are pyelonephritis, pneumonia, peritonitis, cholangitis, cellulitis, meningitis, or abscess formation at any site. Many of these infections are nosocomial and occur in patients hospitalized for other medical problems. In patients with normal host defenses, a site of infection is identified in most patients. In neutropenic patients, however, a clinical site of infection is found in less than 50% of septic patients, probably because small, clinically inapparent infections in skin or bowel can lead to blood stream invasion in patients with inadequate circulating neutrophils.

DEFINITIONS

Considerable effort has been directed toward identifying septic patients early in their clinical course, when therapies are most likely to be effective. Definitions have incorporated manifestations of the systemic response to infection (fever, tachycardia, tachypnea, and leukocytosis) as well as evidence of organ system dysfunction (cardiovascular, respiratory, renal, hepatic, central nervous system, hematologic, or metabolic abnormalities). The most recent definitions (Table 96–1) use the term *systemic inflammatory response syndrome* (SIRS) to emphasize that sepsis is one example of the body's inflammatory responses that can be triggered not only by infections but also by noninfectious disorders, such as trauma and pancreatitis (Fig. 96–1).

Sepsis is severe and has a poorer prognosis when it is associated with organ dysfunction, hypoperfusion (lactic acidosis, oliguria, or altered mental status), or hypotension (septic shock). Septic shock is defined as sepsis-induced hypotension that persists despite adequate fluid resuscitation and is associated with hypoperfusion abnormalities or organ dysfunction. In clinical practice, many patients with these signs and symptoms are receiving vasopressor and/or inotropic agents and are no longer hypotensive when they manifest hypoperfusion abnormalities or organ dysfunction, but they still are considered to be experiencing septic shock.

PATHOGENESIS

Microorganisms proliferate at a nidus of infection; they may invade the blood stream, resulting in positive blood cultures, or they may grow locally and release their structural components, such as teichoic acid antigens from staphylococci, endotoxins from gram-negative organisms, or exotoxins (e.g., toxic shock syndrome toxin-1, or TSST-1) synthesized and released by the microorganisms (Fig. 96–2). These organism-derived products can stimulate the release of a large number of endogenous host-derived mediators from plasma protein precursors or cells (monocytes-macrophages, endothelial cells, neutrophils, and others).

The endogenous mediators can produce profound physiologic effects on the vasculature and organ systems. When released in small amounts, these mediators result in beneficial effects such as regulating immune function, killing bacteria, and detoxifying bacterial products. However, an exaggerated response can result in harmful effects. Some of these effects stem from direct mediator-induced injury to end organs. However, a portion of the organ

Table 96–1 ■ DEFINITIONS OF SEPSIS

Infection: A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Bacteremia: The presence of viable bacteria in the blood.
Systemic inflammatory response syndrome: The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:
- Temperature >38° C or <36° C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg (<4.3 kPa)
- White blood cell count >12,000 cells/mm³, <4000 cells/mm³, or >10% immature (band) forms

Sepsis: The systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection:
- Temperature >38° C or <36° C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg (<4.3 kPa)
- White blood cell count >12,000 cells/mm³, 4000 cells/mm³, or >10% immature (band) forms

Severe sepsis: Sepsis associated with organ dsyfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.
Septic shock: Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Hypotension: A systolic blood pressure <90 mm Hg or a reduction >40 mm Hg from baseline in the absence of other causes for hypotension.
Multiple organ system failure: Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Adapted from American College of Chest Physicians Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864, 1992.

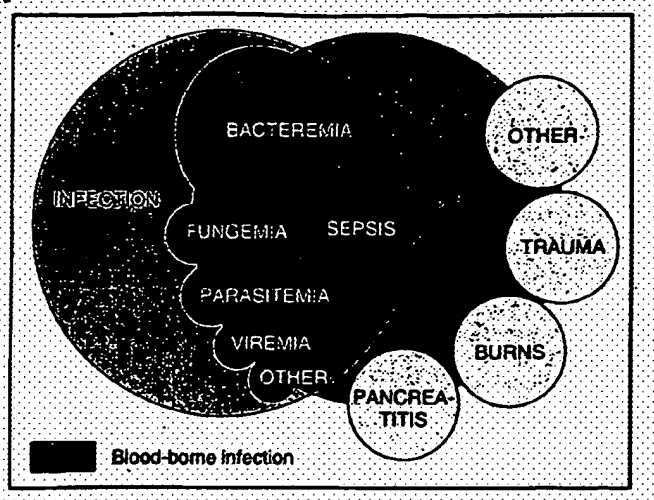

FIGURE 96–1 ■ Interrelationships among systemic inflammatory response syndrome (SIRS), sepsis, and infection. (From American College of Chest Physicians Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864, 1992.)

dysfunction is probably due to mediator-induced abnormalities in vasculature, resulting in abnormalities of systemic and regional blood flow. Although certain mediators are undoubtedly more important than others in producing sepsis, probably dozens of organism- and host-derived mediators interacting, accelerating, and inhibiting one another are responsible for the pathogenesis of septic shock.

Approximately 50% of patients who have hypotension secondary to sepsis and who are admitted to an intensive care unit survive; the other 50% develop refractory hypotension or multiple organ system failure and die from progressive septic shock. Early and throughout the course of most of these patients, cardiovascular evaluation reveals a low systemic vascular resistance and a high cardiac output—the hyperdynamic response to sepsis. Despite this elevated cardiac output, cardiac performance is abnormal, with a decreased ventricular ejection fraction and a dilated ventricle. In approximately 20% of patients, progressively diminished cardiac performance results in an abnormally low cardiac output. In nonsurvivors, organ system dysfunction progresses to multiple organ system failure, manifested by further myocardial dysfunction, adult respiratory distress syndrome (ARDS), acute renal failure, hepatic failure, and disseminated intravascular coagulation (DIC). Death results from progressive hypotension or complete failure of one or more organ systems.

MICROORGANISM-DERIVED MEDIATORS. A number of molecules can initiate the pathway leading to septic shock. Certain microorganisms synthesize and release exotoxins that can activate the cascade. Examples include toxin A produced by *Pseudomonas aeruginosa* and TSST-1 produced by staphylococci. More frequently, the structural components of the microorganism initiate the sequence. The polysaccharide surface of *Candida albicans*, the teichoic acid antigens of staphylococci, and the polysaccharide capsule of *Streptococcus pneumoniae* can all initiate the sepsis pathway.

However, endotoxin—the distinctive lipopolysaccharide (LPS) associated with the cell membrane of gram-negative organisms—represents the classic example of an initiator of the septic shock pathogenetic cascade. The endotoxin molecule consists of an outer core with a series of oligosaccharides that are antigenically and structurally diverse, an inner oligosaccharide core that has similarities among common gram-negative bacteria, and a core lipid A that is highly conserved across bacterial species. The lipid A, which is responsible for many of the toxic properties of endotoxin, has been the focus of attempts to synthesize nonactive analogues or develop inhibitors to interfere with the septic process.

Administering endotoxin to a variety of animals results in a cardiovascular response very similar to human septic shock. Administering a very small dose of purified endotoxin to normal humans results in fever, mild constitutional symptoms, and a cardiovascular pattern qualitatively similar to that of spontaneous sepsis: tachycardia, decreased systemic vascular resistance, and depressed ventricular ejection fraction. In septic patients, detectable plasma levels of endotoxin are correlated with positive blood cultures, decreased systemic vascular resistance, depressed ventricular ejection fraction, and lactic acidemia. In patients with positive blood cultures and septic shock, detectable plasma endotoxin is associated with increased mortality (39% versus 7% for those without endotoxemia). Thus, endotoxin is an important mediator in many (though not all) septic shock patients; however, routine measurement of circulating plasma endotoxin is not prognostically reliable enough to be used clinically.

CYTOKINES. The monocyte-macrophage plays an important role in the body's response to infection or endotoxin. Endotoxin can stimulate monocytes to produce tumor necrosis factor (TNF), interleukin-1 (IL-1), and other cytokines. Serum contains a protein, the LPS-binding protein, that can bind the lipid A portion of endotoxin. When complexed with this protein, LPS can bind the CD14 receptor and stimulate the monocyte to produce cytokines at concentrations far below those required for stimulation by LPS alone.

Cytokines are 15- to 30-kD polypeptides that have profound immune regulatory and physiologic effects. Considerable evidence suggests that cytokines can enhance host defense mechanisms (e.g., stimulating lymphocyte progenitor cells, enhancing neutrophil oxidative burst) but also can produce harmful effects. In animal models, administering TNF results in a cardiovascular pattern of shock that is very similar to clinical sepsis. Anti-TNF antibodies have prevented shock and death from endotoxin and live organism challenge in animals. TNF produces vascular dilation and myocardial cell depression in biologic models, suggesting its involvement in these sepsis-associated physiologic abnormalities. Although TNF probably has a central role in mediating sepsis-induced injury, it most likely does not work alone. TNF and IL-1 have been shown to work synergistically to produce hypotension in animals, and additive or synergistic actions among a number of cytokines probably account for many sepsis-associated abnormalities.

MYOCARDIAL DEPRESSION. A number of animal models suggest the presence of a circulating myocardial depressant as the possible cause of ventricular dysfunction during sepsis. Human studies have documented the presence of circulating myocardial depressant activity that correlates temporally with the reduced ventricular ejection fraction (Table 96–2). Recent data suggest that this depression may result from a synergistic effect of TNF and IL-1 on myocardial cell contraction.

ENDOTHELIAL CELLS AND NEUTROPHILS. A number of mediators, including LPS and TNF, can cause endothelial cells to express adhesion receptors (selectins) and can activate neutrophils to express ligands for these receptors. Neutrophils must stick to the endothelial cell surface for their adherence, margination, and migration into foci of inflammatory tissue. Blockage of the adhesion process with monoclonal antibodies prevents tissue injury and improves survival in certain animal models of septic shock.

NITRIC OXIDE. In response to LPS, TNF, and other mediators, endothelial cells and macrophages can release nitric oxide, which causes smooth muscle cell relaxation and potent vasodilation. Inhibition of nitric oxide production with competitive inhibitors of nitric oxide synthase increases blood pressure in animals with endotoxin shock, suggesting that nitric oxide is partially responsible for the hypotension associated with sepsis. Although inhibition of nitric oxide restores blood pressure, such inhibition may also reduce tissue blood flow.

COMPLEMENT, KININ, AND THE COAGULATION SYSTEM. Endotoxin can activate the complement cascade, usually via the alternative pathway, and result in the release of the anaphylotoxins C3a and C5a, which can induce vasodilation, increased vascular permeability, platelet aggregation, and activation and aggregation of neutrophils. These complement-derived mediators may be responsible in part for the microvascular abnormalities associated with septic shock. Endotoxin can also result in the release of bradykimin via the activation of factor XII (Hageman factor), kallikrein, and kininogen. Bradykinin is a potent vasodilator and hypotensive agent. LPS activation of factor XII also leads to intrinsic and (through macrophage and endothelial cell release of tissue factor)

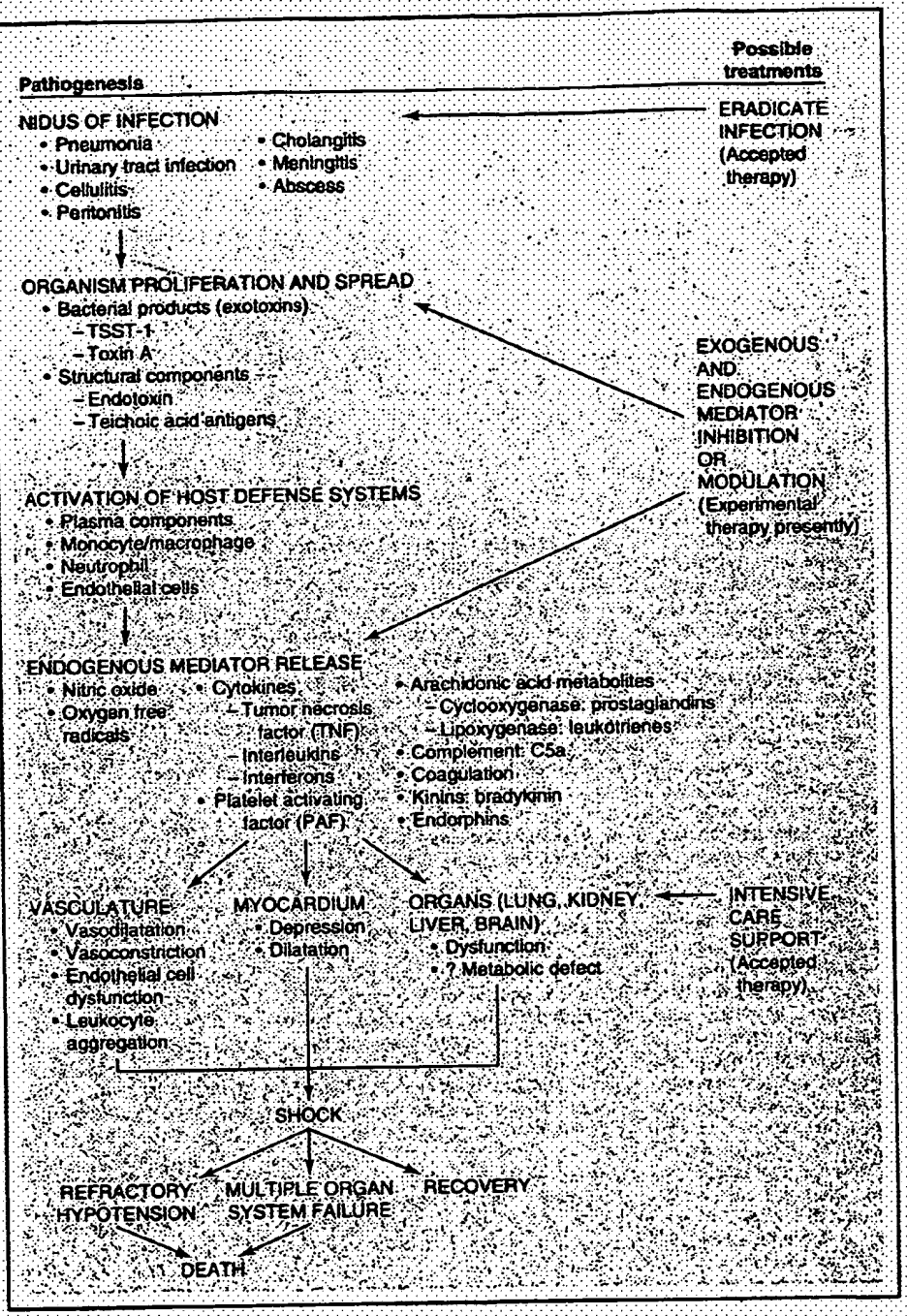

FIGURE 96–2 ■ Pathogenesis and possible treatment strategies in sepsis and septic shock. TSST-1 = toxic shock syndrome toxin-1.

extrinsic coagulation pathway activation, which may result in consumption of coagulation factors and DIC. TNF also activates the extrinsic pathway and may contribute to these coagulation abnormalities.

ARACHIDONIC ACID METABOLITES. Different metabolites of the arachidonic acid cascade are known to cause vasodilation (prostacyclins), vasoconstriction (thromboxanes), platelet aggregation, or neutrophil activation. In experimental animals, inhibition of cyclooxygenase or thromboxane synthase has protected against endotoxin shock. Elevated levels of thromboxane B_2 (TBX_2) and 6-ketoprostaglandin $F_{1\alpha}$ (the end product of prostacyclin metabolism) are present in patients with sepsis. A number of cytokines can cause release of these arachidonic acid metabolites from endothelial cells or leukocytes. In addition to nitric oxide, some arachidonic acid products are partially responsible for the vasodilation that is characteristic of septic shock.

OPIOID PEPTIDES. In certain animal models of endotoxin challenge, administering an endogenous opioid antagonist, such as naloxone, can reverse hypotension. The role of endogenous opioids in clinical septic shock is unclear.

CARDIOVASCULAR DYSFUNCTION

Shock is classically defined as inadequate perfusion of tissues that results in cell dysfunction and, if prolonged, cell death. This definition adequately describes shock due to the hypovolemic, cardiogenic, and vascular obstructive mechanisms (see Chapter 94)

Table 96-2 ■ CARDIOVASCULAR RESPONSE TO SEPTIC SHOCK: A REPRESENTATIVE EXAMPLE

	ACUTE PHASE (HYPOTENSION AND REDUCED SYSTEMIC VASCULAR RESISTANCE)	RECOVERY PHASE (NORMOTENSION)
Mean arterial pressure (mm Hg)	40	75
Central venous pressure (mm Hg)	2	5
Cardiac output (L/min)	11.25	5.25
Heart rate (bpm)	150	70
Stroke volume (mL)	75	75
Systemic vascular resistance (dyne·sec·cm^{-5})	270	1067
Left ventricular volumes (mL):		
Diastole	225	125
Systole	150	50
Ejection fraction (%)	$\frac{225\ mL - 150\ mL}{225\ mL} = 33$	$\frac{125\ mL - 50\ mL}{125\ mL} = 60$

that result in reduced cardiac output and poor tissue perfusion. In these forms of shock, systemic vascular resistance is elevated as a compensatory mechanism to maintain blood pressure, and pulmonary artery oxygenation is reduced, reflecting enhanced extraction of oxygen from erythrocytes by hypoperfused peripheral tissues.

However, sepsis results in a much more complex form of shock. The onset of sepsis is frequently accompanied by hypovolemia due to both leakage of plasma (capillary leak) into the intravascular space and arterial and venous vasodilation. Correcting this hypovolemia by aggressive volume replacement results in a decreased systemic vascular resistance, increased or normal cardiac output, tachycardia, and elevated oxygen content in the pulmonary artery blood—the hyperdynamic shock syndrome. This hemodynamic pattern has been termed *distributive shock* to indicate the presumed maldistribution of systemic blood flow leading to the high blood oxygen content returning to the right side of the heart. Before volume resuscitation, patients with septic shock may manifest features of both hypovolemic and distributive shock, that is, a mixed form of shock.

Despite the elevated or normal cardiac output in volume-resuscitated septic shock, ventricular function is abnormal, as reflected by decreases in ventricular ejection fraction and stroke work and increases in end-diastolic and end-systolic volumes. In survivors, this cardiovascular dysfunction is reversible and returns to normal 5 to 10 days after septic shock. Certain hemodynamic patterns have prognostic implications. At disease onset, a lower heart rate predicts survival, probably reflecting less severe disease. Serial hemodynamic measurements demonstrate that normalization (within 24 hours) of either the elevated cardiac index or tachycardia is associated with survival, whereas persistence of the hyperdynamic state correlates with nonsurvival.

Vascular dysfunction is one of the most prominent physiologic and pathologic findings in septic shock. Patients usually manifest an overall decrease in systemic vascular resistance, reflecting widespread systemic vasodilation; however, some localized vascular beds are constricted. The decreased extraction of oxygen in the systemic circulation suggests that oxygen is not reaching or is not being used by cells. One hypothesis argues that vascular abnormalities (vasodilation, vasoconstriction, leukocyte aggregation, and endothelial cell dysfunction induced by complex interactions among the mediators summarized previously) result in decreased tissue perfusion. A second hypothesis argues that a direct mediator-induced cellular metabolic abnormality causes the failure of oxygen uptake. A central question in the pathogenesis of sepsis is whether decreased perfusion due to microvascular dysregulation is a primary cause or only an associated event in sepsis-induced organ failure.

Another method of judging whether a vascular perfusion abnormality is important in septic shock is to evaluate the relationship between oxygen delivery and oxygen consumption. In patients with cardiogenic or hypovolemic shock, when tissue hypoperfusion clearly occurs, increases in oxygen delivery result in increased consumption until hypoperfusion is reversed and oxygen consumption plateaus. Some investigators have argued that septic shock (especially with ARDS) is characterized by a pathologic delivery-consumption relationship in which consumption continues to increase (and not plateau) with increased delivery, suggesting the presence of a perfusion abnormality that can be overcome by increasing delivery to a supranormal range. This observation is controversial, and animal experiments have yielded conflicting results. Although some initial clinical studies reported improved outcomes when oxygen delivery was increased, subsequent larger clinical trials comparing conventional strategies with strategies designed to increase oxygen delivery to a supranormal range have failed to demonstrate a survival advantage for the supranormal approach. Some studies suggest that pretreatment of critically ill surgical patients with supranormal oxygen delivery may provide some benefit, but further studies will be necessary to resolve these controversial findings.

CLINICAL MANIFESTATIONS AND DIAGNOSTIC EVALUATION

Sepsis and septic shock produce three categories of clinical manifestations (Fig. 96–3). First, the patient usually manifests symptoms and signs related to the primary focus of infection. If it is pneumonia, then the patient usually has cough, dyspnea, and productive sputum; if a urinary tract infection is the focus, then flank pain and dysuria would be expected. A careful history, physical examination, and directed imaging and laboratory studies will reveal the probable infectious focus in most patients. However, elderly, debilitated, and immunosuppressed patients may not exhibit the usual localizing clinical signs. In some patients, especially those with severe neutropenia, no site is identified. Second, patients usually manifest one or more signs of the systemic inflammatory response. Fever is the most characteristic and is frequently accompanied by shaking chills. A significant proportion of patients (perhaps 15%) will be hypothermic (<36.5°C or 97.6°F) or normothermic, especially the elderly, debilitated, or immunosuppressed. Elderly patients may present with tachypnea-induced respiratory alkalosis and mental status changes as the only signs of sepsis. Third, septic patients may develop evidence of shock, such as hypotension, lactic acidemia, and progressive organ system dysfunction. A variety of organs will show characteristic dysfunction (see Fig. 96–3).

The diagnosis of sepsis is confirmed by culturing pathogenic organisms from blood or from the likely site of infection. Blood cultures are positive in only 40 to 60% of patients with clinical manifestations of septic shock, probably owing to the intermittent nature of the bacteremia and the high incidence of prior antibiotic administration. A Gram stain from an abscess, empyema, or other usually sterile site can provide invaluable early diagnostic information.

TREATMENT

Septic shock can be managed effectively at three points along the pathogenetic sequence. First, the infection site can be eradicated with antimicrobials, surgical drainage, or both. Second, the serious disturbances in cardiovascular, respiratory, and other organ system

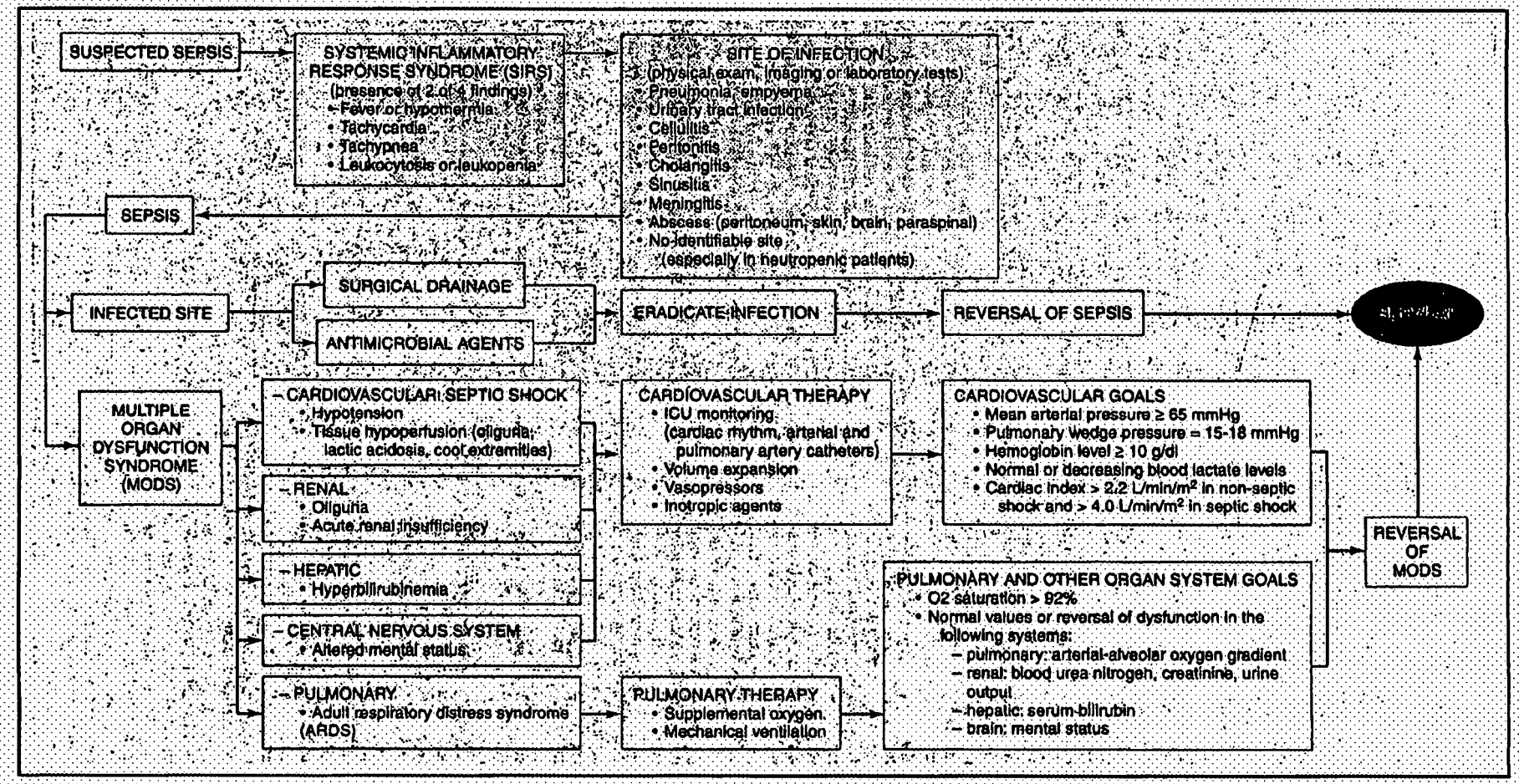

FIGURE 96-3 ■ Algorithm for diagnostic evaluation and management of sepsis and septic shock.

physiology can be reversed in an intensive care unit. Third, the toxic mediators of sepsis can be inhibited or modulated.

ANTIMICROBIAL THERAPY. Shock secondary to sepsis is a very major disease that should be treated aggressively. When the diagnosis is seriously entertained, blood cultures (usually three) and cultures of relevant body fluids and exudates should be obtained rapidly. Several large retrospective trials have provided convincing evidence that early appropriate antimicrobial therapy (i.e., the pathogen has in vitro sensitivity to the chosen antibiotic regimen) is associated with significantly improved patient survival. Once a specific pathogen is isolated, the antimicrobial spectrum can be narrowed.

A broad-spectrum regimen with activity against gram-positive and gram-negative organisms should be chosen. Generally, drugs should be administered intravenously at maximum recommended dosages, and bactericidal agents are preferred over bacteriostatic agents. Knowledge of the most likely organisms to infect a given site and the local institution's bacteriologic sensitivity and resistance patterns is important in choosing the best initial antimicrobial regimen. Many physicians favor using at least two effective antimicrobial agents in neutropenic patients with gram-negative pneumonia and a two-drug synergistic combination when treating serious enterococcal infection (see Chapter 314). Anaerobes are likely pathogens in intra-abdominal infections, aspiration pneumonia, and abscesses. Intravascular catheter infection should raise the possibility of methicillin-resistant staphylococcal infection and the need for vancomycin therapy. In up to one third of patients, especially those who are neutropenic, no organism or source will be identified. Such patients require a broad-spectrum regimen effective against gram-positive, gram-negative, and anaerobic organisms such as (1) vancomycin, gentamicin, and metronidazole or (2) ceftazidime and gentamicin. The need for early antifungal therapy with amphotericin B should be considered in neutropenic, immunosuppressed patients and in those unresponsive to antibacterial regimens.

THERAPY FOR SHOCK. Before the general availability of intensive care units, gram-negative bacteremic shock had a higher than 90% mortality. Now, about 50% of such patients survive, largely because of treatment in intensive care units, in which cardiac rhythm, blood pressure, cardiac performance, oxygen delivery, and metabolic derangements can be monitored and abnormalities can be corrected. Adequate oxygenation and ventilatory support are critical goals of therapy and can be achieved with supplemental oxygen and, if necessary, mechanical ventilation and positive end-expiratory pressure (PEEP). Although no prospective trial has evaluated outcomes with and without intensive care unit support, two retrospective studies have reported a significantly reduced mortality in septic shock when patients were managed with aggressive hemodynamic support by critical care personnel. A controlled, prospective trial of intensive care unit support has been conducted in dogs with gram-negative sepsis; survival was increased only in the animals that received both antibiotic therapy and cardiovascular support.

Patients with septic shock who remain hypotensive after a 1- or 2-L volume resuscitation should have arterial and pulmonary artery catheters placed to allow serial evaluations of blood pressure, ventricular filling pressures, cardiac output, and oxygen delivery. The pulmonary artery catheter is especially useful for initial assessment and titration of fluid status but should be removed as soon as the patient's hemodynamic stability can be maintained without it in the pulmonary artery. Initial emphasis should be placed on restoring mean blood pressure to greater than 65 mm Hg. Aggressive volume resuscitation using blood (if hemoglobin is less than 10 g/100 mL), colloid (if serum albumin is less than 2 g/100 mL), or crystalloid (in all other patients) should be instituted to raise the pulmonary artery mean wedge pressure to 15 to 18 mm Hg. If hypotension persists, dopamine (low-dose and then, if necessary, higher doses up to 20 μg/kg/minute) should be administered. In patients who are unresponsive to dopamine, norepinephrine should be infused to raise mean blood pressure to higher than 65 mm Hg. Patients who require high doses of norepinephrine may benefit from concomitantly administered low-dose dopamine to enhance renal blood flow. Once blood pressure is adequate, attention should be turned to cardiac output and oxygen delivery. Although the role of achieving very high levels of oxygen delivery and consumption is controversial, most investigators favor inotropic support (with dobutamine, if necessary) to offset the myocardial depression of sepsis and to maintain a cardiac index in the high normal range (higher than 4.0 L/minute/m^2). Serial measures of lactate, urine output, and organ function can provide good measures of patient prognosis.

MEDIATOR INHIBITORS. Treatments that inhibit the action or formation of mediators are being developed. High-dose corticosteroids can inhibit mediator release and improve survival in some animal models of endotoxemia. However, three prospective, randomized clinical trials have demonstrated convincingly that corticosteroids do not improve survival in human septic shock. Small trials in certain diseases—meningococcal meningitis in children and typhoid fever—suggest that they may have a therapeutic role in these specific infections but are not indicated in the usual patient with septic shock.

Another therapeutic strategy has been to inhibit endotoxin. Large, controlled clinical trials using a polyclonal antisera and monoclonal antibodies raised against endotoxin revealed no overall survival benefit but benefit in some subgroups. However, the patients in whom the treatment was likely to be effective (e.g., patients with blood cultures positive for gram-negative organisms) cannot be identified early in the course of infection, when therapy must be initiated. Further, the clinical characteristics of the patients who benefited from the treatment varied in the different trials. For these reasons, none of these antiendotoxin preparations has been approved for use in the United States. More potent pharmacologic inhibitors of endotoxin may prove efficacious in future trials.

Monoclonal antibodies to TNF, which have the theoretic advantage of efficacy against gram-positive and fungal as well as gram-negative infections, are undergoing clinical trials at present. An IL-1 receptor antagonist has been synthesized in large quantities and has shown therapeutic efficacy in animal models of sepsis; in preliminary clinical trials, certain subgroups of septic patients appear to benefit from IL-1 receptor blockade. Inhibitors of nitric oxide synthesis raise blood pressure in animal models of septic shock and show some promise in reducing the toxic effects of the sepsis cascade; however, none has proved to reduce mortality in prospectively defined groups of septic patients. Thus, mediator inhibition or modulation is not accepted therapy of sepsis and septic shock.

A word of caution is warranted regarding mediator inhibitor therapy. The pathogenesis of septic shock is very complex and highly interdependent; many of the components represent the body's appropriate compensatory response to sepsis and therefore have salutary effects. For example, in dogs with gram-negative sepsis, plasma exchange increases mortality, presumably because removal of all circulating mediators is more harmful than beneficial. In some clinical trials using TNF inhibitors, high-dose inhibition was associated with increased mortality. All these mediator inhibitors must be evaluated carefully with rigorous animal and human trials to ensure that they improve morbidity and mortality.

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97 DISORDERS DUE TO HEAT AND COLD

Ernest Yoder

TEMPERATURE HOMEOSTASIS

Humans as homeothermic organisms depend on a highly integrated neuroendocrine system to maintain their thermal homeosta-

microbial therapy must be evaluated in the light of available microbiologic data and new culture data sought to explain the failure of therapy. Explanations for fever other than failure of antimicrobial therapy must be considered; these range from a new superimposed infection to a non-infectious complication or a drug reaction. Additionally, reasons for the failure of appropriate therapy must be considered. These include (1) the presence of anatomic abnormalities or an obstructed drainage system; (2) an undrained abscess; (3) the presence of a foreign body or the equivalent (renal calculus, osteomyelitic sequestrum) at the site of infection; (4) impaired host defenses; (5) infection in infarcted tissue; (6) emergence of resistance in the original pathogen or a resistant superinfecting organism; and (7) suboptimal antibiotic therapy because of poor penetration to the site or physical inactivation (local pH) of the antibiotic. The physician must search diligently to explain and correct the antibiotic failure.

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319 PNEUMOCOCCAL PNEUMONIA

Richard J. Duma

DEFINITION. Pneumococcal pneumonia is an acute, suppurative infection of the lungs produced by an encapsulated bacterium, *Streptococcus pneumoniae* (pneumococcus). It is the most commonly occurring bacterial pneumonia in the world; in the United States, an estimated 150,000 to 570,000 cases occur annually.

MICROBIOLOGY. Virulent *S. pneumoniae* organisms are encapsulated, gram-positive cocci about 0.8 μm in diameter that occur in chains (streptococci) or pairs (diplococci) (see Color Plate 9E). When in pairs, cocci are characteristically lancet shaped; i.e., each coccus is pointed at the end like the tip of a lance, and the bases are in juxtaposition. The capsule, which is a complex polysaccharide that varies in chemical composition and thickness, is not seen with Gram staining but may be recognized by negative staining (e.g., with India ink or methylene blue). In purulent clinical specimens, some pneumococci stain negatively rather than positively with Gram stain because aging, exposure of the cell wall to a variety of destructive host enzymes (e.g., lysozyme), and/or inhibition of cell wall synthesis by antibiotics (e.g., penicillin) result in incomplete or abnormal bacterial cell walls that no longer retain the iodine-fixed crystal violet stain.

Pneumococci are fastidious, facultative bacteria that grow best in the presence of blood or serum and in air supplemented with 10% carbon dioxide. Because they are fermentative and lactic acid is the usual end product, concentrations of glucose in the culture media must be controlled and should not exceed 1%. In addition, because they produce hydrogen peroxide (H_2O_2) but not catalase, the addition of a catalase source (e.g., red blood cells) enhances growth. Viability is reduced by drying, a low pH (<6.5), and prolonged incubation.

On blood agar after overnight incubation at 37° C, colonies generally appear mucoid, glistening, and dome shaped and are surrounded by an area of greening (α-hemolysis) within the blood agar. With continued incubation, as aged bacteria undergo autolysis, the colony domes of highly encapsulated strains collapse centrally and appear umbilicated. An important biologic feature that distinguishes *S. pneumoniae* from other streptococci is its bile solubility or susceptibility to surface-active agents such as sodium deoxycholate and ethyl hydrocuprein chloride (optochin). The latter agent (optochin) is incorporated into a standardized 5-μg disk and used worldwide to identify pneumococci rapidly. However, because optochin-resistant pneumococci occasionally occur and some non-pneumococcal α-hemolytic streptococci are optochin sensitive, for purposes of species determination, the usefulness of this biologic property may be questioned.

Pneumococcal virulence is often studied in the mouse because this animal is highly sensitive to encapsulated pneumococci (with the exception of type 14). Indeed, the sensitivity of mice to encapsulated pneumococci may be used for rapidly and selectively isolating virulent pneumococci from sputum specimens or from clinical materials containing other bacteria. If injected into the peritoneal cavity of the mouse, an exudate containing pneumococci may be harvested in 24 hours.

Unlike many other streptococci, particularly those belonging to Lancefield group A, and unlike other pyogenic bacteria that produce pneumonia, *S. pneumoniae* does not produce any major toxins, particularly none that are tissue destructive. Some strains may elaborate hyaluronidase, and all contain pneumolysin, a hemolytic cytotoxic protein, released when the organism undergoes autolysis, that disrupts the respiratory epithelium and slows ciliary movement.

The most important factor defining virulent *S. pneumoniae* is the presence of a high-molecular-weight complex polysaccharide capsule, which is a potent inhibitor of neutrophil phagocytosis. At least 84 different immunogenic types of capsules exist, and two different nomenclatures (Danish and American) are used to number them (which is often a source of confusion). Antigenically distinct capsules are easily identified with polyvalent antisera in an agglutination or precipitin test or by the Neufeld quellung reaction, a rapid test based on visualization of refractile swelling of the capsule after application of a polyvalent or monovalent type-specific antiserum to the bacterium in question. Non-encapsulated pneumococci, which are generally avirulent, do not react with antipolysaccharide antisera. Although identification of pneumococcal capsular antigen in certain body fluids or secretions may suggest active pneumococcal infection (see below), immunologic tests to detect such antigens must be interpreted with caution because antibodies against some pneumococcal capsular serotypes cross-react with polysaccharides of other streptococci (particularly group B), *Haemophilus influenzae* type B, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* species, and even human ABO blood group isoantigens.

Capsular polysaccharides consist of repeating di- or penta-oligosaccharides, some of which contain large proportions of acid constituents such as cellobiuronic, hexuronic, and pyruvic acid. Most are linear, although some are branched, and their antigenicities result principally from oligosaccharide epitopes of no more than six or seven sugar residues. The frequency of capsular types observed varies with time, geography, and the age of the patient; for example, types 6, 14, 18, 19, and 23 are common in infants and children, whereas types 1, 2, 3, 5, and 8 are common in adults.

The susceptibility of pneumococci to most chemotherapeutic antibacterials, especially to the β-lactams (except the monobactams), is generally good; however, this pattern appears to be rapidly changing. For penicillin G, the antibiotic against which all other antibacterials are compared, *susceptibility* is defined as inhibition of growth of pneumococci at a concentration of less than 0.1 μg/mL.

Table 319-1 • MIC_{90} OF SOME COMMONLY USED β-LACTAM ANTIBIOTICS AGAINST PENICILLIN-RESISTANT PNEUMOCOCCI

ANTIBIOTIC	MIC_{90} (μg/mL)	
	Intermediate Penicillin Resistance	High-Level Penicillin Resistance
Ampicillin	0.5	8
Oxacillin	4.0	31
Methicillin	—	64
Carbenicillin	32.0	64
Ticarcillin	64.0	128
Piperacillin	1.0	8–16
Mezlocillin	1.0–2.0	8–15
Azlocillin	1.0	16
Cephalothin	1.0	8–31
Cefaclor	4.0–16.0	16
Cefonicid	16.0	16
Cefoxitin	4.0–8.0	32–125
Cefamandole	0.5–2.0	8–31
Cefuroxime	0.25–0.44	—
Cefotaxime	0.125–1.0	1–4
Ceftriaxone	0.12–0.5	1
Ceftazidime	3.2–32.0	64
Cefoperazone	1.0–2.0	2–16
Moxalactam	2.0–4.0	128
Imipenem	0.06–1.0	1–2

MIC_{90} = minimal inhibitory concentration at which 90% of strains are susceptible.
Adapted with permission from Klugman KP: Pneumococcal resistance to antibiotics. Clin Microbiol Rev 3:171, 1990.

(referred to as the *minimum inhibitory concentration* [MIC]). However, since 1968, when penicillin-resistant strains were first identified in clinical isolates from Australia, a significant but variable percentage of isolates are defined as *intermediately* (i.e., MIC, ≥ 0.1 to < 2.0 μg/mL) or *highly resistant* (i.e., MIC, ≥ 2.0 μg/mL). Strains that are highly resistant to penicillin G are resistant to a wide array of other β-lactams (Table 319–1) but may be susceptible to the 3rd-generation cephalosporins ceftriaxone and cefotaxime and to the carbapenems. Presently, all pneumococci are susceptible to vancomycin and teicoplanin, agents generally reserved for serious, life-threatening infections (e.g., meningitis).

Other effective antibacterials often used clinically include the macrolides (e.g., erythromycin), lincosines (e.g., clindamycin), some of the newer fluoroquinolones (e.g., levofloxacin), chloramphenicol, and the rifamycins (e.g., rifampin). However, strains that are highly resistant to penicillin G (see Table 319–1) are often resistant to many of these antibacterials, especially the macrolides. Resistance of pneumococci to β-lactams is *not* due to bacterial production of a β-lactamase or a cephalosporinase and is *not* plasmid mediated; rather, it results from transformation of previously susceptible strains by DNA from penicillin-resistant, related streptococci and from point mutations of host chromosomal elements and/or newly acquired transposons. These newly formed genetic elements dictate the production of aberrant target membrane, penicillin-binding proteins that have little or no affinity for penicillin G or other β-lactams, thus rendering the penicillins ineffective.

Pneumococci are relatively resistant to aminoglycosides; in fact, gentamicin may be incorporated into primary culture media for selective isolation of pneumococci from sputum because it suppresses the growth of concurrent bacteria. Furthermore, in some studies more than 50% of pneumococcal isolates are resistant to tetracyclines.

EPIDEMIOLOGY. Pneumococcal pneumonia is generally a community-acquired, sporadic disease that occurs most often during the coldest months of the year. More recently, it has been recognized as an occasional cause of nosocomial pneumonia. The vast majority of cases occur after aspiration of "normal" oropharyngeal secretions that may contain encapsulated pneumococci, followed by an inability to clear such secretions; thus oropharyngeal carrier rates of pneumococci are important in the dynamics of acquiring pneumococcal pneumonia, its spread, and its frequency of occurrence within a population.

Because most data referable to oropharyngeal carrier rates were obtained before the use of pneumococcal vaccine, colonization rates with (or carriage of) certain serotypes and the relative importance of factors that have an impact on carriage must be interpreted with caution. Nevertheless, in longitudinal, pre-vaccine studies of pneumococcal oropharyngeal carriage by people living in temperate zones, serotypes with USA numbers of 23 or less are most frequently encountered, further suggesting that humans are infected by their own endogenous flora inasmuch as more than half the cases of pneumococcal pneumonia and bacteremia are caused by these strains. Clustering of one serotype within a family commonly occurs, and carriage rates do not appear to be affected by gender. Rates of carriage are higher in children, particularly those of preschool age, than in adults; and among adults, rates are highest in those intimately exposed to pre-school children. Oropharyngeal carriage appears to be highest during the coolest months of the year (fall, winter, and early spring), when respiratory infections are common, and spread may be enhanced during respiratory tract infections by pneumococcus or certain respiratory viruses such as rhinovirus. Although the prevalence of oropharyngeal carriage in the surrounding community or within households affects the risk of individual acquisition, crowding does not appear to be important. The duration of oropharyngeal carriage of a particular serotype ranges from 2 weeks to years, the mean being 6 to 8 weeks. Reacquisition of the same serotype commonly occurs. In children but not usually adults, initial acquisition within a family setting is frequently associated with rises in homotypic serum antibody and occasionally with illness.

Although epidemics of pneumococcal pneumonia may occur, they are *rare* and generally appear in special populations at high risk for pneumococcal disease, such as domiciliary populations of alcoholics, institutionalized elderly, Navajo Indians, New Guinea highlanders, Alaskan natives, and South African gold miners. In studies of ambulatory adult populations, a variety of risk factors appear to predispose to the development of pneumococcal infections (Table 319–2).

IMMUNOLOGY. In non-immunized, untreated patients, specific anticapsular humoral antibody (IgM and IgG) can be detected in the blood 5 to 10 days after infection and correlates with the clearance of pneumococci and eventual recovery. Both classic and alternative-pathway complement (C'3) and type-specific opsonizing antibody, principally IgG (IgG1 in children and IgG2 and IgG4 in adults), enhance the phagocytosis and intracellular killing of pneumococci by polymorphonuclear leukocytes and alveolar macrophages, the major host defense mechanism for eradicating pneumococci. Patients with deficiencies of biologically active IgM, IgG, and to a lesser degree, IgA (particularly secretory) are more susceptible to pneumococcal pneumonia and other pneumococcal infections than are normal persons without such deficiencies. In normal persons, once specific anticapsular antibodies form, they generally persist for life.

If pneumococci escape this host defense mechanism, they may

Table 319-2 • RISK FACTORS OR UNDERLYING CONDITIONS PREDISPOSING TO THE DEVELOPMENT OF PNEUMOCOCCAL PNEUMONIA OR SERIOUS PNEUMOCOCCAL INFECTIONS

Age (extremes)
Alcoholism
Bone marrow transplantation
Bronchiectasis
Cerebrovascular occlusions or severe neurologic impairment
Chronic bronchitis
Chronic lymphocytic leukemia
Chronic obstructive pulmonary disease
Cirrhosis or chronic liver disease
Complement deficiency (particularly C'3 and C'4)
Conditions associated with aspiration (e.g., seizures)
Congestive heart failure
Dementia
Diabetes mellitus
Immunologic deficiencies (acquired, hereditary, or iatrogenic)—humoral (IgG or IgA) or cellular (e.g., AIDS)
Institutionalization, homelessness, day care centers
Malignancy (particularly solid tumors of the lung)
Multiple myeloma
Nephrotic syndrome
Neutropenia
Smoking
Splenic dysfunction (e.g., in sickle cell disease) or asplenia
Viral diseases, especially influenza

enter the blood stream via lymph channels and the thoracic duct and produce bacteremia. Clearance from the blood also depends on opsonization via type-specific antibodies and activated complement; however, liver and spleen macrophages rather than polymorphonuclear leukocytes are principally responsible for removing pneumococci from the blood. Thus splenectomy or cirrhosis of the liver rather than neutropenia increases the risk for pneumococcal bacteremia, dissemination, and death.

PATHOGENESIS AND PATHOLOGY. Most cases of pneumococcal pneumonia result from the aspiration of oropharyngeal material containing indigenous, virulent pneumococci into terminal bronchioles and alveoli, followed by atelectasis and an inability to clear bacteria from these sites. Although microaspiration is a natural event that occurs commonly, pneumonia in normal individuals seldom results because pulmonary bacterial clearance and/or local host defense mechanisms are generally adequate and intact and are not defective or suppressed. These important defense mechanisms, which serve as either a barrier against or a clearance for bacteria, are the epiglottic reflex, ciliary escalator and mucous blanket, secretory and humoral immunoglobulins, surfactant, alveolar macrophage and polymorphonuclear leukocyte activity, and lymphatic drainage. When these mechanisms are blunted or overwhelmed by aspirated noxious material, by large inocula of pneumococci, by a highly virulent strain, and/or by material containing additional pathogens, pneumonia may result. In addition, once infection occurs, further atelectasis from inspissated material may result.

After pneumococci establish themselves in the lung, the first visible evidence of an inflammatory response is localized capillary dilatation and hyperemia, the appearance of serous edema within alveoli, followed by margination, diapedesis, and chemotaxis of polymorphonuclear cells induced by immunoglobulins and/or activated complement. In addition, pneumococci produce a soluble, oxygen-labile 53-kd toxin, pneumolysin, that is cytotoxic to pulmonary endothelial cells and may be important in the early phases of pneumonia and entry of *S. pneumoniae* into the blood. Fluid-filled alveoli enhance the passage of bacteria through the pores of Kohn and into terminal bronchioles, with spread to contiguous, uninfected alveoli forming the advancing margins of the disease. If clearance and host immune mechanisms are adequate at this stage, the infection may resolve. However, if not, the disease may spread until the pleura and interlobar fissures are reached and consolidation with dense infiltrates of polymorphonuclear leukocytes and extravasated red blood cells occurs (see Color Plates 9A to 9C).

Pneumococcal pneumonia may involve an entire lobe (lobar pneumonia), multiple lobes (multilobar pneumonia), or just segments of a lobe and produce a patchy area (or areas) of pneumonia (pneumonitis). At times, infection spreads concentrically from bronchi (bronchopneumonia), a pattern occasionally seen in infants and the elderly. In the central and oldest portions of infection, consolidation with massive numbers of polymorphonuclear leukocytes predominates, whereas peripheral to this are new areas of hemorrhage, infiltrating polymorphonuclear cells, and edema. Early pathologists referred to these areas in the lung as "gray hepatization" and "red hepatization," respectively, because of the gross resemblance of involved lung to liver tissue (see Color *Plate 9A*). In fully developed, untreated pneumococcal pneumonia, all stages of the cellular inflammatory process may be present.

In 5 to 10% of patients, infection may extend into the pleural space and result in an *empyema*, or in 15 to 25% of patients, bacteria may enter the blood stream (*bacteremia*) via the lymphatics and thoracic duct. Invasion of the blood stream by pneumococci may lead to serious metastatic disease at a number of extrapulmonary sites (Table 319–3), the most important and most frequent of which is the subarachnoid space (*meningitis*.) Other infections that may occur from bacteremic spread are *septic arthritis, pericarditis, endocarditis* (infection of the heart valves), and in patients with ascites, *peritonitis (spontaneous bacterial peritonitis.)* In addition, pneumococci may concurrently infect other tissues or organs such as the sinopulmonary system, air sinuses (*sinusitis*), mastoids (*mastoiditis,*) ears (*otitis media,*) conjunctivae (pyogenic *conjunctivitis*), epiglottis (*epiglottiditis*, particularly in infants), or rarely the soft tissues of the neck or retropharyngeal area (*Ludwig's angina.*)

CLINICAL FINDINGS. The features of acute bacterial pneumonia caused by *S. pneumoniae* may be highly variable, depending on when the patient is seen by the physician in the course of the disease, whether or not bacteremia and/or dissemination has occurred, the patient's age, whether or not effective antibiotics were previously administered, the presence or absence of satisfactory host defenses, and the existence of risk factors for dissemination of pneumococci (e.g., asplenia, neutropenia, and agammaglobulinemia). The manifestations may be mild or explosive and rapidly lethal. Classically, the onset of acute pneumococcal pneumonia is sudden and characterized by an abrupt occurrence of cough, chills, high fever (up to 40 °C), myalgias, tachypnea, shallow respirations, tachycardia, weakness, and often frank rigors. Initially the cough may be productive of scant mucopurulent or blood-streaked sputum; later (after 24 to 48 hours) it may be thick, purulent, frankly bloody or rust-colored, and consistent with an alveolar, hemorrhagic, exudative process. If the infecting pneumococcus is highly encapsulated, a gelatinous, blood-tinged sputum may be seen. The presence of pleuritic pain is specific clinical evidence that the pneumonia is probably bacterial and, in the presence of most of the above findings, probably pneumococcal.

Table 319–3 • CONCURRENT OR COMPLICATING PNEUMOCOCCAL INFECTIONS OCCURRING IN PNEUMOCOCCAL PNEUMONIA

Otitis media
Sinusitis/mastoiditis
Conjunctivitis (suppurative)
Epiglottiditis
Tracheobronchitis
Pleuritis (empyema)
Soft tissue cellulitis (Ludwig's angina)
Pericarditis*
Endocarditis*
Meningitis*
Arthritis (septic)*
Peritonitis (in presence of ascites)*

*Usually blood-borne.

Patients with pneumococcal pneumonia are generally diaphoretic and, in addition, may be dehydrated and hypotensive. Anorexia, nausea, and vomiting are common. If allowed to continue untreated, single-lobe disease may progress to multilobe involvement, and the patient may become dusky, cyanotic, and confused. If bacteremia occurs, chills and rigors may persist, and rarely shock, disseminated intravascular coagulopathy (DIC), and/or adult respiratory distress syndrome may supervene and ultimately lead to the patient's death.

A history is frequently elicited of a recent upper respiratory or viral-like illness that has occurred before the appearance of clinical pneumonia, especially during the winter months, when influenza is common. Risk factors for aspiration, such as alcoholism, seizures, or vomiting, or for acquiring pneumococcal pneumonia may be present (see above).

On physical examination, the acutely ill patient is tachypneic and may be observed to use accessory muscles for respiration (intercostal, abdominal, and sternocleidomastoid) and even to exhibit nasal flaring. If pleuritic pain is severe, reflex splinting of the ipsilateral thorax is observed. Fever and tachycardia are present, and although hypotension may occur, frank shock is unusual, except in the later stages of infection or DIC.

Auscultation of the chest reveals bronchovesicular or tubular breath sounds and wet rales over the involved lung. As consolidation occurs, vocal and tactile fremitus is increased; however, if a concurrent pleural effusion is present, breath sounds and fremitus may be diminished or absent. A localized, grating pleural friction rub may occasionally be heard.

Examination of the upper respiratory passages may be helpful in suggesting a diagnosis of pneumococcal pneumonia. For example, in children the absence of exudative pharyngitis and the presence of otitis media might suggest pneumococcal involvement. In older children and adults, the air sinuses and/or mastoids may be acutely infected. (However, these infections can also occur with streptococcal, staphylococcal, and *H. influenzae* pneumonia.)

Evidence of extrapulmonary infections may be present, particularly in untreated disease lasting more than 48 hours; for example, signs of meningeal irritation (stiff neck, Kernig's or Brudzinski's sign) with abnormalities in mentation may suggest meningitis; the appearance of pathologic heart murmurs, splenomegaly, and heart failure may be evidence of endocarditis; or the presence of pain,

swelling, tenderness, heat, and possibly redness in one or more joints may point toward a septic arthritis of hematogenous origin.

Additional findings unrelated to pneumonia per se but related to sepsis and/or toxicity may be noted: a paralytic ileus with abdominal pain, distention, and loss of bowel sounds; mild jaundice from reactive hepatitis or intrapulmonary hemorrhage; frank shock; purpuric lesions resulting from DIC; or symmetrical gangrene and purpura of the fingers and/or toes (*purpura fulminans*) associated with bacteremia.

LABORATORY FINDINGS. The peripheral white blood cell (WBC) count is often two to three times the normal value; however, in alcoholics or immunosuppressed patients, it may be normal or low. Of more value is the WBC differential, which consists predominantly of bands and polymorphonuclear leukocytes (left shift). If DIC is suspected, thrombocytopenia, pleomorphism of red blood cells (schistocytes and helmet cells), prolonged prothrombin and partial thromboplastin times, and hypofibrinogenemia and circulating fibrin split products may be present.

In some patients, total bilirubin and hepatic cellular enzyme levels may be slightly elevated. Because dehydration and hypovolemia commonly occur (secondary to fever, diaphoresis, nausea, and vomiting), the hemoglobin, hematocrit, and serum sodium level may be elevated. When pneumonia is the dominant clinical event, arterial blood gas studies, which reflect pulmonary function and compensatory events, usually reveal hypoxemia (low PO_2), hypocapnia (low PCO_2), and alkalosis (blood pH >7.4) resulting from hyperventilation and shunting. However, if frank shock intervenes, a metabolic acidosis may result (blood pH <7.4); if it is not corrected, death may follow.

Good posteroanterior and lateral chest radiographs are important to obtain, initially to confirm the presence and to ascertain the extent and radiographic character of the pneumonia and secondly, to determine whether underlying predisposing pulmonary diseases are present such as bronchiectasis, bronchial obstruction, emphysema, tumor, or tuberculosis. In severely dehydrated or profoundly neutropenic or immunodeficient patients, early inflammatory infiltrates may not be seen radiographically or may be patchy and irregular in appearance, but after hydration or restoration of circulating levels of inflammatory cells, patterns of lobar consolidation may become apparent.

Characteristically, in immunocompetent patients with untreated, frank pneumococcal pneumonia, chest radiographs reveal a lobar distribution and an air space (or alveolar exudative) pattern of disease with an air bronchogram effect. However, if prior, partially effective antibiotic usage has occurred, the pattern may be atypical, and a lobar distribution may be the exception rather than the rule. Interlobar fissures may bulge because of the considerable fluid content within the involved lung associated with large amounts of capsular material. In severe cases, more than one lobe may be involved (multilobar pneumonia). In 30% of cases, a pleural effusion may be present and may be readily detected by a lateral decubitus film. Such effusions may be sterile and represent parapneumonic collections of fluid, or occasionally they may be infected with pneumococci, in which case they are called *empyemas*.

If blunting of the costophrenic angle is noted radiographically and the finding is believed to represent an effusion, at least 300 to 500 mL of fluid is probably present and thoracentesis is indicated. Unless contraindicated, *every pleural effusion associated with an acute bacterial pneumonia in which the etiology of the pneumonia is unclear should be tapped and the fluid studied for microorganisms* (see Color Plate 9*D*). Ordinarily, fluid removed from the pleural space is sterile, so any bacteria seen on a Gram stain or cultured from the fluid represent pathogens until proved otherwise.

Other important laboratory studies *that must be obtained early in the patient's work-up* are routine cultures of the blood, microscopic examination of a Gram stain and culture *of purulent material from the site of infection* (alveoli, bronchi, or lung), and examination of any infected material that can be removed from a secondarily infected extrapulmonary focus. Results of blood cultures may not be available for 18 to 24 hours and thus cannot assist the physician in making a presumptive diagnosis or in selecting appropriate initial chemotherapy. Often, in asplenic patients a high-grade bacteremia occurs, so examination of the peripheral WBC smear or the buffy coat for pneumococci may be useful.

Microscopic examination and cultures of expectorated purulent sputum from a patient with acute bacterial pneumonia are essential if a correct presumptive etiologic diagnosis is to be made and an appropriate antibiotic is to be given. Ideally, these tests should be done before therapy is initiated; however, significant delay in instituting therapy should not be permitted. Attention must be given to obtaining a diagnostically useful sputum sample; that is, material must be purulent to be presumed to be from the site of infection. Salivary or oropharyngeal gross contamination of the sample should be avoided.

In a patient with the clinical picture of acute bacterial pneumonia, the finding of gram-positive diplococci in expectorated sputum that contains ≥50 polymorphonuclear cells per 100× field (purulent sputum) and few (<10 squamous cells per 100× field) or no squamous epithelial cells (which indicates little or no oropharyngeal contamination of the specimen) is strong presumptive evidence of pneumococcal pneumonia.

Cultures of expectorated sputum are also important but are not without problems; for example, because *S. pneumoniae* is fastidious, it may fail to grow in culture, but negative culture results do not exclude its presence. In addition, pneumococci may be overlooked because they may be overgrown by other organisms or mixed with similar-appearing, non-pneumococcal, α-hemolytic streptococci, which are normally present in oropharyngeal secretions. On the other hand, because *S. pneumoniae* is often present normally in the oropharynx, its growth from sputum, especially from expectorated sputum, may not be indicative of pneumococcal disease. Perhaps the main value of securing a sputum culture is to confirm or question observations made from the Gram stain and, if pneumococci (and/or other bacteria) are ultimately isolated, to perform antibiotic susceptibility testing.

If the patient is unable to expectorate purulent sputum for microscopic examination and culture and if other infected materials (e.g., pleural or joint fluid) are not available or are negative for pneumococci, various procedures for obtaining pus from the infected lung must be considered. Cough can be induced by having the patient inhale an aerosol of warm 3% NaCl; a plastic catheter can be inserted into the trachea via the nose or throat and suction applied; a direct transtracheal needle and catheter aspiration may be performed (a procedure not without complications); the patient may undergo endoscopy (provided that arterial PO_2 is ≥ 50 mm Hg), and alveolar washings or bronchial brushings may be obtained; or rarely, direct aspiration of the pneumonic infiltrate through the chest wall with a long, "skinny" needle (22 gauge) may be used (a procedure also not without risks). Open-lung biopsies for pneumococcal pneumonia are not indicated, although they may be for certain complications, ill-defined superinfections, or underlying diseases. In any acute bacterial pneumonia, the guiding principles for deciding what procedure, if any, to use for obtaining purulent sputum from the involved lung for diagnostic study are as follows: (1) if expectorated sputum is satisfactory (i.e., purulent and relatively free of contaminating oropharyngeal material), further efforts to obtain pus from the deeper recesses of the lung are probably not necessary; (2) if additional procedures are necessary, one should initially select the procedure that is least traumatic and invasive and is risk-free and then proceed, if necessary, in stepwise fashion to the next least invasive, risk-free procedure until satisfactory material is obtained; (3) one should not delay more than several hours before beginning chemotherapy, and if the patient is extremely ill, one must rely on clinical judgment and probabilities and not delay treatment, and (4) one must make every effort to identify the etiologic agent (or agents) responsible for the pneumonia early in the course of the illness because once this goal is realized, the chances of managing the patient successfully are markedly enhanced.

A variety of other tests may be applied to sputum specimens to identify pneumococci in acute bacterial pneumonia, but in skilled hands, few, if any are better, less costly, easier to do, and more informative than the Gram stain. All tests done on sputum possess a similar problem in interpretation, namely, determining whether the bacteria present in the sample are responsible for the pneumonia observed. If blood or pleural fluid cultures are subsequently positive for *S. pneumoniae*, the etiologic agent is confirmed, although the presence of additional pathogenic bacteria within the

lung may not be entirely excluded because blood or pleural fluid cultures may rarely yield other bacteria (polymicrobial infection) in addition to pneumococci.

Detection of pneumococcal capsular antigen generally requires the presence of approximately 10^5 bacteria per milliliter, about the same concentration required to observe an average of one bacterium per 1000× field (or an oil-immersion field on a standard light microscope) on a Gram stain. Cross-reactions with other antigens of other bacteria are frequent, and with certain serotypes, false-positive results are common. Perhaps the greatest value of capsular antigen detection is to confirm the presence of pneumococci in patients who have been partially treated and in whom sputum cultures may be negative and a Gram stain may reveal few, if any intact bacteria.

Colony counts of bacteria from bronchoalveolar lavage washings obtained during endoscopy are seldom available early in the course of illness. Specimens must be obtained with a special cuffed endoscope so that oropharyngeal contamination does not occur with insertion of the scope. Generally, counts of colony-forming units of bacteria higher than 10^3 to 10^4 per milliliter of fluid removed are considered significant, but such counts are not invariably found.

DNA hybridization studies may be performed directly on the sputum, but as with capsular antigen detection, adequate numbers of bacteria must be present for the test to be positive. Use of the polymerase chain reaction may amplify pneumococcal DNA and improve the potential for detection; however, such enhanced sensitivity may lead to false-positive results caused by very small numbers of contaminating pneumococci.

Elastase or elastin fibers in sputum may suggest the presence of a gram-negative bacillary necrotizing pneumonia, particularly that caused by *Pseudomonas*, but this test is of little value in the diagnosis of pneumococcal pneumonia (other than that the test should be negative) because necrosis of tissue is not produced by pneumococci.

DIFFERENTIAL DIAGNOSIS. (See also Chapter 82 and chapters dealing with the specific organisms.) The clinical picture and many of the routine laboratory and radiographic features associated with pneumococcal pneumonia are often indistinguishable from those of other acute bacterial pneumonias. Thus collecting appropriate microbiologic data is essential if the correct etiologic diagnosis is to be made.

In adults, the second most common community-acquired, acute bacterial pneumonia is that caused by *H. influenzae*. Gram stain of purulent sputum from such patients often reveals myriads of tiny gram-negative coccobacilli, with the observation of an occasional filamentous form. Such an infection often occurs in a patient with chronic bronchitis or chronic obstructive pulmonary disease and is usually due to non-encapsulated *H. influenzae* (as opposed to highly encapsulated, serotype B strains commonly associated with young children).

Staphylococcus aureus is another bacterium occasionally producing acute pneumonia, but when this kind of pneumonia is community-acquired, it usually occurs during or just after an epidemic of viral influenza. In the hospital setting, *S. aureus* may be seen year-round because it is a commonly occurring nosocomial infection. If a highly virulent, toxin-producing strain is responsible, the "toxic shock syndrome" may be observed. On a Gram stain of purulent sputum, clusters and characteristic tetrads of gram-positive cocci are seen. Late in the clinical course, abscess formation or destruction of the lung occurs.

Group A streptococci (*S. pyogenes*) also produce acute pneumonia, and in such instances the patient may be more toxic appearing than the extent of involvement of the lung might suggest. Classically, a small, peripherally located, wedge-shaped infiltrate is seen, and a thin, watery, serosanguineous, pleural effusion is present. A radiograph of the chest may suggest pulmonary infarction. An upper respiratory tract infection, particularly an exudative or erythematous pharyngitis or tonsillitis (especially in children), may be present, and an erythematous rash produced by streptococcal erythrogenic toxin (scarlet fever) may be seen. Gram staining of purulent sputum usually reveals numerous short chains of gram-positive cocci or diplococci. Thus the Gram stain may not differentiate group A streptococcal from pneumococcal pneumonia.

Branhamella catarrhalis may produce acute pneumonia, but this pneumonia usually occurs in the elderly, particularly in those with chronic bronchitis or obstructive lung disease. It is a relatively benign infection when compared with those produced by other pyogenic bacteria and is rarely, if ever associated with bacteremia. A Gram stain of purulent sputum is again important, and the diagnosis should probably be made only when numerous gram-negative coccobacilli are seen in the absence of other potentially pathogenic bacteria. *Neisseria meningitidis* (meningococci) is morphologically similar to *B. catarrhalis* and must also be included in the differential diagnosis. However, in meningococcal disease, patients are generally young adults, and the infection is associated with significant toxicity.

Gram-negative bacilli, particularly those belonging to the family Enterobacteriaceae (e.g., *E. coli, Klebsiella, Enterobacter, Serratia,* and *Proteus*), must also be considered as causative agents in the differential diagnosis of pneumococcal pneumonia, particularly if the patient is debilitated and residing in a nursing home or similar institution and certainly if the patient is hospitalized. Aerobic gram-negative bacilli are often responsible for nosocomial pneumonias but infrequently for community-acquired pneumonias, because gram-negative bacilli rarely colonize the oropharynx of otherwise healthy people in the community but they are common oropharyngeal residents in debilitated, hospitalized, or institutionalized patients. In addition, the patient in question may exhibit certain risk factors associated with invasion by gram-negative bacilli, such as the receipt of prior antibiotics, corticosteroids, inhalation therapy, or tracheostomy, and the existence of profound neutropenia or severe debilitation. The pneumonic process is usually necrotizing, and gas formation may be detected on radiographs. A Gram stain of purulent sputum usually reveals many large, bipolar-staining gram-negative rods. Elastin fibrils may also be seen on a KOH preparation of sputum from the site of infection.

Anaerobic bacteria may also produce acute suppurative pneumonia. Those most frequently involved are *Bacteroides* species (usually *B. melaninogenicus*), *Peptostreptococcus,* and *Fusobacterium.* Frequently, anaerobic infections are polymicrobial and may include bacteria other than strict anaerobes (e.g., *S. aureus*). The occurrence of anaerobic infection is usually preceded by gross aspiration and is enhanced if the individual has anaerobic oral infections or solid tumors of the oropharyngeal structures or tracheobronchial tree. The clinical features of anaerobic pleuropneumonic disease may be indolent rather than abrupt, and it may be accompanied by pus that has a fetid and nauseating odor. Necrosis of the lung with gas formation is often noted.

Mycoplasma pneumoniae, Chlamydia, and *Legionella* may also produce acute pneumonias, which are usually best described as atypical. With mycoplasmal pneumonia, patients are ordinarily young, and prolonged communicability, especially within households, may often be documented. The clinical, radiographic, and pathologic features are usually those of an interstitial pneumonia rather than lobar consolidation and an alveolar exudative process. Serum cold agglutinin levels may be elevated, and the disease is rarely, if ever fatal. Chlamydial pneumonia, especially that caused by *C. psittaci,* is contracted from infected psittacine birds, whereas *C. pneumoniae* or the TWAR agent is acquired from other infected humans. *C. pneumoniae* is the most common species producing chlamydial pneumonia in humans, and the clinical picture is usually that of pharyngitis, often with laryngitis, and segmental pneumonia of a single lobe without pleural effusion. Seroepidemiologic studies reveal a higher prevalence of antibodies in males than females and in older adults than children. Legionnaires' disease, which may be produced by a variety of *Legionella* species but principally by *L. pneumophila,* is associated with considerable systemic toxicity (nausea, vomiting, and diarrhea) and may be very difficult to differentiate from pneumococcal pneumonia. However, in the temperate zones, community-acquired Legionnaires' disease usually occurs in the warmer months or summer; patients are typically male construction workers and smokers in their 50s whose clinical manifestations include fever, chills, myalgias, headache, dry non-productive cough, and non-specific pulmonary infiltrates. Anti-*Legionella* fluorescein-labeled antibodies, which may be used to examine sputum for *Legionella,* as well as antigen detection techniques applied to the urine, may be helpful in the early diagnosis of this disease.

Patients with the acquired immune deficiency syndrome (AIDS) and acute pneumonia present considerable diagnostic problems. Al-

though pneumococcal pneumonia and infections from other encapsulated bacteria occur with greater frequency in patients with AIDS than in normal individuals, pneumocystosis and cytomegalovirus pneumonia, as well as tuberculosis, occur frequently and must thus be excluded.

Finally, not only does pneumonia caused by microbes other than the pneumococcus have to be considered in the differential diagnosis, but also a variety of non-infectious conditions may mimic the clinical picture of pneumococcal pneumonia. Pulmonary infarction, with emboli (e.g., in right-sided endocarditis) or without emboli (e.g., in sickle cell anemia), may present a considerable diagnostic challenge, even after differential lung scanning and pulmonary angiography. Chemical pneumonitis, localized or diffuse (Mendelson's syndrome) and often caused by aspiration of gastric juice of low pH, may also be difficult to differentiate from pneumococcal or other bacterial pneumonias; however, in the absence of antibiotic therapy, a Gram stain of purulent sputum consistently reveals few or no bacteria.

TREATMENT. All patients with suspected pneumococcal pneumonia should be treated as promptly as possible with an effective antimicrobial agent. One should not wait for cultural confirmation of the diagnosis to initiate therapy. Although some patients may recover without antibacterial therapy, effective antimicrobial agents reduce morbidity, mortality, and complications.

If penicillin resistance, especially high-level resistance, is not considered a problem, penicillin G is considered the therapy of choice. Blood and tissue levels of penicillin G in excess of the MIC for susceptible strains (< 0.1 μg/mL) are easily achieved with doses of 1.2 to 2.4 million U/day. If the infecting strain is of intermediate resistance (MIC ≥0.1 to <2.0 μg/mL), penicillin G can still be successfully used; however, doses approximating 6 to 12 million U/day need to be used. For patients who are believed to be allergic to penicillin, one may select a first- or second-generation cephalosporin or erythromycin, clindamycin, or a fluoroquinolone.

With the advent of high-level penicillin resistance, different strategies of therapy may have to be devised on the basis of susceptibility to non-penicillin G, β-lactams (see Table 319–1) and to non-β-lactam antibacterials (Table 319–4). In many parts of the United States and the world, cefotaxime and ceftriaxone resistance is approaching 25% in respiratory tract pneumococcal isolates. Nevertheless, if the presence of high-level penicillin resistance is considered a good possibility, ceftriaxone, 1 to 2 g every 24 hours, or cefotaxime, 1 to 2 g every 6 hours, perhaps combined with a macrolide, fluoroquinolone, rifamycin, or lincomycin, may need to be used until susceptibility data become available. However, if a serious, life-threatening infection such as meningitis caused by high-level penicillin-resistant pneumococci is present, vancomycin plus ceftriaxone or cefotaxime need to be used.

Initial therapy should be parenteral to ensure delivery and adequate serum and tissue levels. If the patient is in shock or has heart failure, the route of delivery should be intravenous. Later in the course of therapy, if the patient's progress is good, the route of administration may be changed to oral. Treatment with any effective agent should be given for at least 5 to 7 days.

Table 319–4 • CRITERIA FOR RESISTANCE OF *STREPTOCOCCUS PNEUMONIAE* TO SOME COMMONLY USED ANTIBIOTICS*

ANTIBACTERIAL AGENT	MIC (μg/mL)
Penicillin G	
Intermediate	≥0.1 to <2.0
High level	≥2.0
Erythromycin	≥1.0
Clindamycin	≥1.0
Levofloxacin	≥8.0
Rifampin	≥4.0
Chloramphenicol	≥8.0

MIC = minimum inhibitory concentration.
*Based on criteria established by the National Committee for Clinical Laboratory Standards (NCCLS). Document M100-S8, vol 18: No 1, Jan 1998, pp 68–69. Wayne, PA.

If effective antibacterial therapy is used, the patient's temperature usually falls to or below normal by crisis within 24 hours. However, in some instances, perhaps because of the nature of the pathology or complications that occur (e.g., pleural effusion), the patient's temperature may fall by lysis over 2 to 3 days. Resolution and recovery from pneumococcal pneumonia generally result in restoration of normal pulmonary architecture. Occasionally, healing may be via fibrosis, in which instance persistence of pulmonary infiltrates on radiographs may be evident for months after clinical recovery.

In addition to effective antibacterial therapy, a variety of supportive measures are generally used in the initial management of acute pneumococcal pneumonia; such measures include bed rest, monitoring vital signs and urine output, inserting a Swan-Ganz catheter to monitor cardiac output, administering an occasional analgesic to relieve pleuritic pain to permit effective breathing and coughing, replacing fluids if the patient is dehydrated, correcting electrolytes, oxygen therapy, and relieving an ileus with nasal gastric suctioning. When relieving pleuritic pain or providing sedation in situations requiring it (e.g., in delirium tremens), care should be taken to not use excessively high doses of analgesics or sedatives that might depress the respiratory center. Intercostal nerve blocks, which do not interfere with the respiratory drive, may be used. If possible, antipyretics should also be avoided because these agents interfere with the evaluation of fever as a measurement of the patient's progress (or lack of).

COMPLICATIONS. Empyema develops in approximately 5% of patients with pneumococcal pneumonia, although sterile pleural effusions commonly develop in a larger percentage (up to 30%). Most effusions resolve with successful antibacterial therapy, although empyemas often require drainage. Empyemas usually consist of thick pus composed of fibrin, serous proteins, large numbers of leukocytes and/or their products, and pneumococci. Initially, such collections may be drained by needle aspiration; however, later, as loculations occur, drainage via chest tubes is usually necessary. Chest radiographs with lateral decubitus films are often useful in the early recognition of pleural effusions; however, at a later time and in the course of removal and follow-up, ultrasonography and/or computed tomography may be necessary. In any acute bacterial pneumonia, pleural fluid that is removed should be subjected to Gram stain, aerobic and anaerobic cultures, pH determination, cell count and differential, protein and sugar analysis, and a lactate dehydrogenase test to determine whether an empyema is present.

If pneumococcal bacteremia occurs, extrapulmonary complications such as *meningitis, septic arthritis,* and *endocarditis* must be excluded because their therapy generally requires higher dosages of antibiotics and, in the case of septic arthritis, may require drainage. A spinal tap with examination of cerebrospinal fluid should be done if meningitis is suspected, and multiple pre-treatment blood cultures and echocardiography of the heart valves should be obtained if endocarditis is suspected. Other complications that might occur are *pyogenic pericarditis,* which may produce tamponade and require drainage, and *peritonitis* in those with ascites (e.g., cirrhosis or nephrotic syndrome).

PROGNOSIS. The case fatality rate for untreated pneumococcal pneumonia is about 25%, whereas in those treated promptly with an appropriate antibiotic, it may be less than 5%. Fatality rates differ considerably among patient groups, depending on such factors as the presence or absence of bacteremia, multilobe or single-lobe involvement, the presence or absence of neutropenia or asplenism, underlying diseases (particularly of the heart or lung), age of the patient (the prognosis being poor at the extremes), complicating extrapulmonary pneumococcal infections (e.g., meningitis), the occurrence of shock, the serotype of pneumococcus responsible (type 3 being highly virulent), delayed therapy, penicillin susceptibility or resistance, and prior immunization with polyvalent pneumococcal vaccine. However, since the advent of penicillin G in the 1940s, despite the advent of a variety of antibiotics, the case fatality rate of pneumococcal pneumonia and bacteremia remains essentially unchanged.

PREVENTION. The most important preventive tool available is polyvalent pneumococcal vaccine. This type-specific vaccine contains 23 antigenic capsular polysaccharides, which in the United States account for up to 90% of bacteremic infections. In immuno-

competent populations, it is estimated to be 79% protective and induces antibodies of the IgG2 and IgG4 subclasses in adults, which enhance opsonization, phagocytosis, and killing of pneumococci by polymorphonuclear leukocytes and fixed macrophages. It is virtually free of life-threatening side effects and obviously cannot produce a pneumococcal infection because it contains no viable, intact pneumococci. Fever, localized swelling, and/or pain at the injection site may develop in about 15 to 30% of patients who receive the vaccine. As with all polysaccharide vaccines, it is not immunogenic below ages 18 to 24 months and is poorly immunogenic in the very elderly and in those with a variety of conditions generally associated with decreased vaccine responsiveness. In normal individuals, if antibodies result from vaccination, colonization, or natural infection, they usually persist for several years and then progressively decline. The vaccine is not associated with a booster effect, probably because it functions as a thymus-independent type 2 antigen. At present, highly immunogenic vaccines in which the capsular antigens are conjugated to proteins are under development. Revaccination of the elderly and other high-risk groups needs to be considered at 3- to 5-year intervals.

The U.S. Public Health Service specifically recommends the currently available pneumococcal vaccine for patients with underlying conditions associated with increased susceptibility to pneumococcal infections or increased risk of mortality from such infections, namely, healthy adults 65 years or older and those with chronic cardiac or pulmonary diseases, anatomic or functional asplenia, chronic liver disease, alcoholism, diabetes mellitus, and cerebrospinal fluid leaks. Perhaps the greatest value of vaccination against pneumococci is to reduce bacteremia, dissemination, and mortality, especially in those with hepatic or splenic dysfunction. Type-specific antibody can be elicited with pneumococcal polysaccharides by subcutaneous vaccination even in splenectomized patients. In addition, recommendations for receiving the vaccine are also made for those with chronic renal failure or those undergoing hemodialysis; for those with Hodgkin's disease, chronic lymphocytic leukemia, multiple myeloma, or AIDS; or for those receiving or about to receive chemotherapy for cancer, organ transplantation, or splenectomy.

Antibiotic prophylaxis with penicillin G or similar agents in otherwise healthy patients with viral upper respiratory infections is not routinely indicated, is not cost-effective, and may only lead to superinfections with antibiotic-resistant bacteria or to adverse side effects from the antibiotic itself. However, in individuals with seriously compromised pulmonary, cardiac, or immune function, an appropriate, narrow-spectrum antibacterial agent (the selection of which depends on anticipated antibiotic susceptibility patterns) may be given in moderate dosages during a viral syndrome for a limited time to reduce the risk of morbidity and mortality from potentially invasive pneumococci. Such prophylaxis may especially apply to those in households where pneumococcal infections recently occurred.

Finally, it should be appreciated that pneumococcal infections, including pneumonia, are not generally acquired by otherwise normal people from exposure to other patients with pneumococcal pneumonia; thus patients with pneumococcal pneumonia do not require isolation, and prophylaxis for medical staff exposed to such infections is not indicated.

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320 MYCOPLASMAL INFECTION

David Schlossberg

BACKGROUND. The mycoplasmas associated with humans include species from the genera *Mycoplasma*, *Ureaplasma*, and *Acholeplasma*. Because these genera all belong to the order Mycoplasmatales in the class Mollicutes, they are collectively called "mollicutes" or, more commonly, "mycoplasmas." Over 150 species are recognized, and they are found in humans, animals, plants, and insects. Most of these organisms are commensals, but some of the human strains are pathogenic; rarely, some of the animal strains infect humans as well.

Mycoplasmas are the smallest free-living organisms. At 200 nm, they approximate the size of the larger viruses. Bound by a triple-layered cell membrane, they have no cell wall (thus the name "mollicute," Greek for "soft skin") and are therefore not seen on Gram stain and cannot be treated with cell wall–active antibiotics such as the β-lactams or vancomycin.

Most mycoplasmas are facultative anaerobes. They grow down into agar and produce a dark center with a light periphery on the surface, the so-called fried-egg colonies. Mycoplasmas are distinguished from bacteria in that they lack a cell wall and cannot produce cell wall precursors and are distinguished from viruses, chlamydiae, and rickettsiae in that the mycoplasmas can grow on cell-free media.

The mycoplasmas of humans are listed in Table 320–1. Some are established pathogens, some are commensals, and some infect immunocompromised patients.

IMMUNOLOGY. Mycoplasmas have a wide range of immunomodulatory effects, including stimulation of T- and B-lymphocyte proliferation, induction of cytolytic activity of macrophages and cytotoxic T cells, stimulation of cytokine production, induction of major histocompatibility complex expression in macrophages and B cells, and production of chemotactic factors, Fc factors, Fc receptors, superantigens, and immunoglobulin proteases. This explosive and varied immunologic activity may contribute to disease expression. It is well known that rheumatoid factor, biologic false-positive tests for syphilis, antinuclear antibodies, and other antibodies sometimes appear in the course of mycoplasmal infection.

MYCOPLASMA PNEUMONIAE. *M. pneumoniae* accounts for 10 to 20% of all pneumonias and for at least half of all pneumonias in children and young adults. Although most cases occur in the first two decades of life, mycoplasmal infection is seen at all ages. *M. pneumoniae* typically causes community-acquired pneumonia, but rare cases of nosocomial acquisition are reported.

Infection with *M. pneumoniae* can occur in any season, with a 4-year periodicity for outbreaks. Because epidemics of pneumonia secondary to other agents usually peak in the winter, it is diagnostically helpful when *Mycoplasma* pneumonia occurs in other sea-

Table 320–1 ■ HUMAN MYCOPLASMAS

ESTABLISHED PATHOGENS	OPPORTUNISTS	COMMENSALS
M. pneumoniae	*M. salivarium*	*M. buccale*
M. hominis	*M. orale*	*M. fauclum*
M. fermentans	*M. genitalium*	*M. lipophilum*
M. urealyticum	*M. pirum*	*M. primatum*
	M. penetrans	*M. spermatophilum*
	M. arginini	*A. laidlawii*
	M. felis	*A. oculi*
	M. edwardii	

Transplants, Lung

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Synonyms and related keywords: lung transplantation, lung transplant, lung transplant complications obstructive pulmonary disease, pulmonary hypertension, cystic fibrosis, idiopathic pulmonary fibrosis, Eisenmenger syndrome, single-lung transplantation, bilateral sequential transplantation, combined heart-lung transplantation, lobar transplantation

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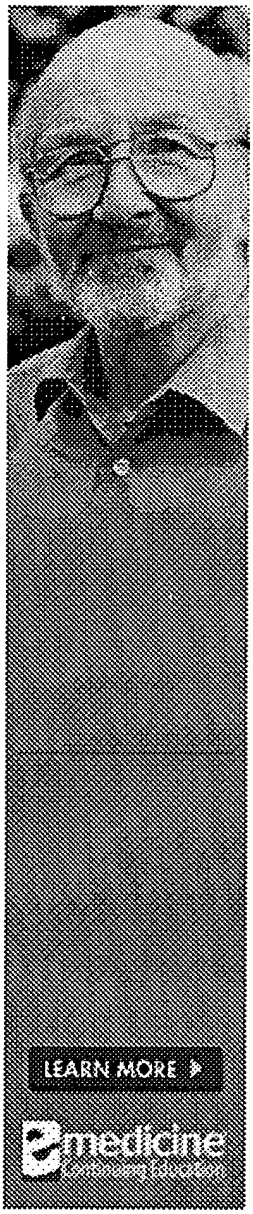
Disclosure



Background

Since the time of the first successful single-lung transplantation in 1983, the number of lung transplant centers as well as organ recipients has continued to rise. This trend coupled with ongoing advances in transplant **medicine** has led to a growing patient subset that provides a unique challenge to the emergency physician.

Pathophysiology

Currently, the most common indication for lung transplantation is chronic obstructive pulmonary disease, but other common indications include pulmonary hypertension, cystic fibrosis, idiopathic pulmonary fibrosis, and Eisenmenger syndrome. Four different surgical techniques are used: single-lung transplantation, bilateral sequential transplantation, combined heart-lung transplantation, and lobar transplantation, with the overwhelming majority of organs procured from deceased donors. The indications for each of these techniques are evolving and are individual to the underlying disease processes.

Medical complications seen in this patient population are variable and most importantly may be a result of surgical complications, **graft rejection**, or immunosuppression, either a direct pharmacologic toxicity or an infectious etiology.

Frequency

At the close of 2005, approximately 3,500 patients were awaiting lung or combined heart-lung transplantation, with transplantation programs available at nearly 70 hospitals nationwide. The mean waiting time for lung transplantation is nearly 14 months, and, in 2005, roughly 1000 patients received a donor organ.

Age

There is **no** defined lower limit of age for lung transplantation, and it is largely limited by the availabilities of suitable-sized donors. Because of the increasingly poor survival with advancing age, the following limits have been recommended: 55 years for heart-lung transplantation, 60 years for bilateral-lung transplantation, and 65 years for single-lung transplantation.

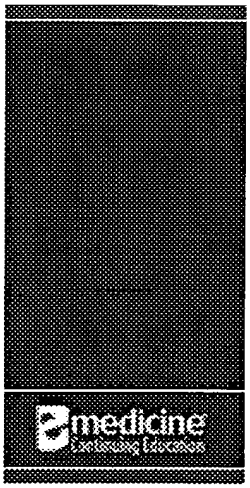
Morbidity/mortality

In 2004, survival rates were approximately 82% at 1 year and 45% at 5 years post transplantation.

Acute surgical complications

Surgical complications following lung transplantation can be further divided into acute and chronic complications. Many of the acute complications occur while the patient is still in the inpatient postoperative setting. Reperfusion edema, a type of noncardiogenic pulmonary edema, is seen in more than 95% of transplanted lungs. Reperfusion edema typically presents as hypoxemia and reduced lung compliance that begins within 24 hours postoperatively and is characterized by diffuse infiltrates on the chest radiograph. The symptoms peak by postoperative day 4-5, and they generally resolve by postoperative day 10. Other acute complications include hemothorax, pleural effusions, chylothorax (a result of perioperative injury to the thoracic duct), and pneumothorax. The ED physician should be aware of these complications, as patients are often discharged with conservative management only for these conditions.

Other acute surgical complications include full or partial dehiscence of the bronchial anastomosis. Bronchial dehiscence results from ischemia of the anastomotic site and is seen in 2-3% of lung transplantation patients. Bronchial dehiscence may present as pneumomediastinum, pneumothorax, or subcutaneous emphysema. Symptoms include tachypnea, shortness of breath, and secondary infections such as mediastinitis cause fevers and leukocytosis. Symptoms range from asymptomatic to fulminant respiratory failure and death depending on the severity of the dehiscence. Diagnosis is made by CT scan, or preferably, by bronchoscopy. Partial dehiscence less than 4 mm is generally managed conservatively, while larger injuries or complete dehiscence requires immediate surgical correction. Patients who present with suspected dehiscence should be admitted for further observation and evaluation.



Delayed surgical complications

Delayed airway complications are commonly seen postoperatively, and they typically present several weeks to months post transplantation. These complications include stenosis of the anastomotic site, formation of granulation tissue, or bronchomalacia. Presenting complaints include dyspnea with exertion, cough, or shortness of breath, and evaluation of the patient may reveal focal wheezing, recurrent lower respiratory tract infection, or diminished pulmonary function tests. Treatment options include dilatation via rigid bronchoscopy or balloon, debridement with laser or cryotherapy, and stent placement, and recently, brachytherapy has been suggested as a potential treatment modality. Resection or retransplantation are rarely indicated and are reserved only for extreme cases. Timeliness for evaluation and treatment of these conditions should be guided by clinical severity and may range from outpatient referral to emergent airway management.

Other considerations

Like any other post-operative patient, lung transplant recipients are at risk for

pulmonary embolus. Recent postmortem studies have shown a high risk for pulmonary embolus and other thromboembolic events. Patients are at greatest risk in the first 30 days posttransplantation, although complications may still occur at any time postoperatively. Recent studies suggest that this high incidence of thromboembolic complications is due to a hypercoagulable state, which is of an unclear etiology.

ED evaluation

The ED evaluation should be flexible and tailored toward the patient's presentation and clinical suspicion for the underlying etiology. In general, the initial workup for surgical complications should include a CBC, chemistry panel, medication levels, a chest radiograph, and possibly a chest CT, especially if pulmonary embolus or bronchial dehiscence is suspected. Chest CT is also useful in evaluating new or changed pleural space diseases. A type and crossmatch may also be indicated.

Further diagnostic testing and intervention should be performed with consultation with the transplant surgeon or pulmonologist. For example, pleural changes, such as thickening, calcifications, or effusions may be seen up to 1 year postoperatively, and if unchanged from prior studies, they may not require any further emergent evaluation. Another example is chest CT evidence of dehiscence or stenosis, which requires bronchoscopy to guide treatment.

Graft rejection may be divided into subcategories: hyperacute, acute, and chronic **rejection**.

Hyperacute graft rejection

Hyperacute, or primary **graft** failure, occurs within 72 hours postoperatively, making it an entity not typically seen by the emergency physician. Primary **graft** failure results from ischemia-reperfusion injury and presents similarly to acute respiratory distress syndrome. Early mortality may reach up to 60%, and patients who survive to hospital discharge additionally have a protracted course of recovery with significant impairments in pulmonary function.

Acute graft rejection

Acute **graft rejection** is characterized by a host T-cell response toward the transplanted organ. The incidence of acute **graft rejection** is highest in the first 3 months, with rare cases occurring 1 year post transplantation. The diagnosis of acute **rejection** is made based on both clinical and histologic criteria. Clinical features are nonspecific and include dyspnea, fever, leukocytosis, nonproductive cough, hypoxemia, or malaise. Chest radiography may show new opacifications or pleural effusions, but findings are often absent after the first month.

The clinical course is variable and depends on the severity of **rejection**; mild cases of **rejection** may even be asymptomatic. Diagnosis of acute **graft rejection** can be confirmed with bronchoscopic lung biopsy, which reveals perivascular lymphocytic infiltrates. Treatment for acute **graft rejection** is high-dose parenteral steroids

(methylprednisolone 0.5-1 g/d IV) and should be started in consultation with a pulmonologist.

Chronic graft rejection

Chronic **graft rejection**, like acute **graft rejection**, is also characterized by both histologic and clinical parameters. Clinically, the symptoms of chronic **rejection** are nonspecific and variable in severity. In mild chronic **rejection**, the patient may present with a nonproductive cough and dyspnea on exertion, and it can progress to dyspnea at rest, productive cough, pseudomonas colonization, and chest radiographic findings of bronchiectasis and air trapping. Histologic changes involve either the vasculature or the airways.

Chronic vascular **rejection** is caused by atherosclerosis of the pulmonary vasculature, while chronic airway **rejection** is caused by bronchiolitis obliterans. Bronchiolitis obliterans occurs more frequently and is the main source of morbidity and mortality in lung transplant patients. Histologically, bronchiolitis obliterans is a dense irreversible scarring of the terminal and respiratory bronchioles, which partially or totally obliterates the lumen of the airway causing a progressive decline in pulmonary function.

Because of the poor sensitivity of transbronchial lung biopsy, perhaps as low as 15-17%, the diagnosis of chronic **graft rejection** is largely clinical. Chronic **graft rejection** is thus defined as an unexplained drop in the FEV1 to a level of 80% or less of the patient's posttransplantation peak value. Other markers, such as interleukin 12 (IL-12) levels in bronchoalveolar lavage fluid and levels of exhaled nitric oxide, are currently under investigation as potential markers. Chronic **rejection** rarely occurs within the first 3 months after transplantation, but its prevalence increases with time. **No** specific treatment exists for chronic **graft rejection**, and efforts are aimed toward immunosuppression and primary prevention.

ED evaluation

The presenting symptoms of allograft **rejection** are nonspecific and may present similarly to pulmonary infections. The two etiologies must be differentiated in order to guide treatment. The ED physician should obtain a chest radiograph, drug levels, CBC, and chemistries and should consider admission for further diagnostic evaluation. Further confirmatory tests may need to be performed for suspected allograft **rejection** such as pulmonary function tests or bronchoscopy in order to obtain bronchoalveolar lavage fluid or transbronchial lung biopsies. Depending on the severity of the patient's presentation, these tests may be performed in the in-patient setting or during close outpatient follow-up. Disposition should be discussed with the pulmonologist or transplant team.

IMMUNOSUPPRESSION-RELATED COMPLICATIONS Section 5 of 8 [Back Top Next]

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Although the first lung transplantation was performed in 1963, the first successful heart-lung transplantation was not performed until 1981. The success of this procedure after nearly 20 years can largely be attributed to the advent of cyclosporine as an immunosuppressive agent. Cyclosporine and the other immune modulators work by preventing host reactivity to the foreign allograft. Since the first

successful transplant, immunosuppression has now become a mainstay of transplant **medicine**. However, the optimal regimen is still controversial. While successful transplantation would not be possible without use of these medications, they themselves pose a risk secondary to both direct toxicity as well as infectious complications. The current goal of immunosuppression is to find the optimal combination of drugs that maintains efficacy but minimizes the toxicity presented by each agent.

Direct drug toxicity

Immunosuppression regimens consist of two phases: induction and maintenance. The induction phase involves the first week immediately post transplantation, while the maintenance phase refers to the long-term immunosuppression required to prevent **rejection** of the allograft. Induction regimens typically involve a calcineurin inhibitor, either cyclosporine or tacrolimus, which blocks production of interleukin 2, causing a decline in T-cell proliferation. This is may be coupled with an antilymphocyte antibody preparation, such as OKT3, which binds to the T-cell receptor complex, or daclizumab and basiliximab, which bind to the T-cell interleukin 2 receptor. Long-term maintenance regimens generally consist of a combination of cyclosporine or tacrolimus, a cell-cycle inhibitor such as azathioprine or mycophenolate mofetil, and a glucocorticoid. Recent studies show promise for inhaled cyclosporine as an effective means for delivering high concentrations to the allograft, leading to reduction of chronic **rejection**.

Detailed information on each of these medications is available elsewhere on this web site; however, the most common side of effects of these medications are listed here. Evaluation of direct drug toxicity will be guided by the patient's regimen.

- Calcineurin inhibitors
    - Cyclosporine (Sandimmune, Neoral, Gengraf), tacrolimus (FK506, Prograf)
    - Side effects - Nephrotoxicity, neurotoxicity, hypertension, hepatotoxicity, hyperlipidemia, hyperglycemia, increased risk of malignancy. Cyclosporine also causes gingival hyperplasia and hirsutism.
    - Drug interaction - These agents are metabolized though the hepatic cytochrome P-450 system. Other medications metabolized through cytochrome P-450 will compete and delay metabolism causing an increased serum level of the calcineurin inhibitor (eg, diltiazem, nicardipine, verapamil, ketoconazole, fluconazole, bromocriptine, metoclopramide, erythromycin). Medications that increase the activity of the cytochrome P-450 system cause a decrease in serum levels (eg, rifampin, phenytoin, phenobarbital, carbamazepine).
- Antilymphocyte antibodies
    - Muromonab-CD3 (OKT3), daclizumab (Zenapax), basiliximab (Simulect)
    - Side effects - Mostly seen with OKT3 and include nausea, vomiting, diarrhea, encephalopathy, noncardiogenic pulmonary edema, fevers, chills, and increased risk of lymphoproliferative disorder.
- Glucocorticoids
    - Methylprednisolone, prednisone
    - Side effects - Hyperglycemia, hypertension, cushingoid features, avascular necrosis of the hip, hyperlipidemia, peptic ulcer disease, altered mental status, osteoporosis.

- Cell-cycle inhibitors
    - Mycophenolate mofetil (CellCept), azathioprine (Imuran)
    - Side effects - Nausea, diarrhea, anorexia, upper GI bleed, myelosuppression. Azathioprine may additionally cause cholestatic jaundice, hepatotoxicity, and alopecia.

Emergency physicians are often faced with the challenge of evaluating the febrile immunosuppressed patient. The emergency physician must be aware of the increased risk of opportunistic infections, the attenuation of the inflammatory response, which may mask the severity of the infectious process; and the fulminant course that these infections may take in an immunosuppressed patient. Although the etiology of infection is unpredictable, certain types of infections are seen more frequently depending on the length of time between the transplant and presentation to the emergency department.

Infection in the first month post transplantation

Infections occurring during the first month post transplantation are generally bacterial and nosocomial in origin. These infections are related to the surgical wound, vascular access catheters, urinary tract infections, and pneumonia are also common. Patients are given prophylactic antibiotics routinely immediately post transplantation, decreasing the rate of nosocomial infections. The causative organisms of these postoperative infections are otherwise identical to those seen in the nonimmunosuppressed postoperative patient, and their evaluation and treatment is also unchanged.

Infection from 1-6 months post transplantation

During this period, the level of immunosuppression reaches its peak, and accordingly, opportunistic infections and viruses pose significant hazards. Opportunistic infections from *Pneumocystis jiroveci,* and *Legionella, Listeria, Aspergillus,* or *Candida* species are more commonly seen, although cases of pulmonary or disseminated *Cryptococcus* species, *Coccidioides immitis,* and tuberculosis have also been reported. During the first 6 months, viral infections also become more significant, and common etiologies include cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes viruses, hepatitis B, and hepatitis C.

Infection with CMV is of particular interest in post–lung transplantation patients. CMV infection occurs in approximately 58-69% of recipient-positive, donor-negative and recipient-positive, donor positive transplants, and is secondary only to bacterial pneumonia in post–lung transplantation infections. The most severe infections are usually primary infections in seronegative recipients. Secondary CMV infection occurs with reactivation of latent disease, which is unmasked with immunosuppression, or it may represent a new infection with a different strain of CMV. CMV most commonly causes pneumonitis, but it may also present as retinitis, hepatitis, colitis, or gastroenteritis.

Clinical presentation of CMV pneumonitis is nonspecific and may include shortness of breath, low-grade fevers, decrease in pulmonary function, and cough. The chest radiographic appearance is similarly nonspecific and may show perihilar infiltrates, interstitial edema, focal consolidation, or pleural effusions. The clinical presentation is similar to that of acute **graft rejection**. The early diagnosis and treatment of CMV infection is imperative, as studies link early CMV infection with the future development of bronchiolitis obliterans and chronic **graft rejection**. The treatment of CMV infection is intravenous ganciclovir. Many transplant centers routinely administer ganciclovir for CMV prophylaxis; however,

concern exists over rising resistance rates.

Infections after 6 months post transplantation

After the 6-month window, patients without evidence of **rejection** can be maintained on low doses of immunosuppressants. These patients have similar rates and types of infections seen in the general population and opportunistic infections are rare. However, patients with evidence of allograft **rejection** must be maintained on higher doses of immunosuppressants, rendering them more susceptible to aggressive and opportunistic infections. These high-risk patients are often placed on lifelong prophylactic medications, such as trimethoprim-sulfamethoxazole or antifungals. Viral infections are also persistent in this time period. Chronic EBV infection is also linked to the development of lymphoma and other posttransplantation lymphoproliferative diseases.

ED evaluation

The ED physician should have a conservative approach to posttransplantation patients presenting to the ED with infections or fevers. A high degree of suspicion must be kept for opportunistic infections; fulminant infections masked by immunosuppressant medications; and noninfectious complications, such as allograft **rejection**. The evaluation should be tailored to the degree of the patient's immunosuppression and potential infectious organisms, which may correlate to the time post transplantation.

Non–transplant-related febrile illnesses should also be considered, such as appendicitis, pyelonephritis, or viral syndromes. Workup may include a CBC with differential, chest radiography, sputum, blood cultures, and/or urine cultures and urinalysis. Patients that are ill-appearing or with a high degree of immunosuppression should be started on broad-spectrum antibiotics. Patients that fail to respond to broad-spectrum antibiotics should also be evaluated for less common etiologies such as viral or fungal infections.Evaluation may include serum CMV or other suspected viral titers, bronchoscopy for bronchoalveolar lavage or tissue evaluation, and/or fungal cultures.

Patients in the first 6 months post transplantation have a high degree of immunosuppression and will likely require admission to the hospital. However, well-appearing patients that are greater than 6 months post transplantation that have had an uncomplicated medical course may potentially discharged home. Because of the complexity of these cases and the potential for morbidity, the evaluation, treatment, and disposition of lung-transplant recipients should be discussed with a pulmonologist or with the transplant team.

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Lung transplant recipients may present to the ED with presentations ranging from the mundane to life-threatening illnesses. A high level of suspicion must be maintained, especially in the severely immunosuppressed. Treatment and evaluation should be guided by clinical presentation, and early consultation with the pulmonologist or transplant team is recommended.

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What is the optimal prophylaxis for treatment of cardiac allogra vasculopathy?

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Abstract

Coronary artery disease in the transplanted heart, also known as cardiac allograft vasculopath (CAV), is one of the major causes of mortality late after transplantation. It affects up to 50% heart transplant recipients within 5 years of surgery. The mechanisms of CAV are multifactor include both immune and nonimmune factors. Ischemia of the graft at the time of transplantat one of the more important nonimmune factors, because this leads to endothelial cell injury. In factors involving cellular and humoral rejection can further insult the vascular endothelial cell leading to a cascade of immunologic responses. The optimal treatment prophylaxis for CAV l been established. The treatment approach to this major post-transplant complication includes modification of risk factors through medical therapies and strategies. The early use of diltiaze and/or pravastatin or simvastatin has been demonstrated to be effective in reducing the develc of CAV, but does not completely prevent it. There are many ongoing studies involving newer immunosuppressive agents that may hold promise for the future.

Keywords: cardiac allograft vasculopathy, heart transplantation, prophylaxis

Introduction

Cardiac allograft vasculopathy (CAV) is an accelerated form of obliterative coronary artery d that occurs in heart transplant recipients and is one of the leading causes of mortality among l term transplant patients. It occurs in 5-10% of heart transplant recipients each year and conse up to 50% of these patients have angiographically confirmed atherosclerosis within 5 years of transplant surgery. As the donor heart is denervated, heart transplant recipients usually have s myocardial ischemia and may present with congestive heart failure symptoms and/or sudden There is no effective treatment for CAV except that of retransplantation. However, because of scarcity of donor organs, retransplantation raises serious ethical questions. Therefore, emphas been placed on prophylaxis, which may be achieved by treating the various risk factors. This manuscript will briefly review the risk factors and the believed pathogenesis of CAV and exp

optimal prophylaxis therapies for this major post-transplant complication.

Background and risk factors

Histologically, CAV is characterized by concentric intimal proliferation and diffuse narrowin the entire length of the vessel, as opposed to the discrete focal lesions usually seen in native c artery disease. Other differences seen in CAV, as opposed to native coronary artery disease, i rapid development (months to years), intact appearance of the elastic lamina, rarity of calcific distal disease more severe than proximal disease, and rarity of the development of collateral v [1].

Numerous risk factors have been associated with the development of CAV. Accumulating dat suggest that this disease process is predominantly immune-mediated. Reported immune risk f include increased levels of cytotoxic B-cell antibodies, increased anti-human leukocyte antige (HLA) antibodies, more acute cellular and humoral (antibody-mediated) rejection, cytomegal infection, sensitization to the monoclonal antibody OKT3, and detection of early and persiste elevated soluble interleukin-2 receptor levels [2]. Many nonimmune risk factors have also bee associated with the development of CAV [3,4]; these include hyperlipidemia, diabetes, recipi and gender, obesity, pretransplant diagnosis, and donor ischemic time.

Among nonimmune risk factors for CAV, cholesterol and triglycerides have been the most re [3,5]. The mechanism by which increased lipids might lead to greater intimal thickness may b linked to an immune process. Oxidized low-density lipoprotein leads to stimulation of macro activation, DNA synthesis in smooth muscle cells, expression of HLA-DR antigens, and inter 2 receptor expression in resting T cells. Activated macrophages and endothelial cells mediate density lipoprotein oxidation, which can stimulate macrophages further to secrete cytokines a growth factors that, in turn, may promote intimal thickening [6].

Historically, the diagnosis of CAV has been made with coronary angiography. But because C concentric, longitudinal, and diffuse, the coronary angiogram may not detect early developme the disease process. The angiogram simply fills the coronary artery with contrast, but does no diffuse thickening in the coronary arterial wall. Therefore, coronary angiography lacks the se necessary for detection of early CAV. Intravascular ultrasound (IVUS) is a new imaging tech that provides quantitative information on vessel wall morphology and lumen dimension [7]. V used in the heart, an ultrasound catheter is moved over a guidewire that has been inserted into coronary artery. An ultrasound transducer at the tip of this catheter obtains a 360-degree view artery intima and media, and the image is recorded on videotape. Quantitative measurements then be made. It has been demonstrated that IVUS can detect severe intimal thickening in pati whose angiograms appear normal. IVUS has been reported to be the gold standard for early d of CAV and for assessment both of prognosis and of the effects of therapy [8,9]. However, co as to the reliability of IVUS in predicting CAV in the long-term has recently arisen. A longitu prospective study of 20 patients studied by IVUS at 2 months, 1 year, 2 years, and 3 years aft transplant demonstrated that in a majority of patients, early intimal thickening in the first yea accompanied by constrictive remodeling (reduced lumen area). Over the subsequent 2 years, constrictive remodeling is seen despite a decrease in intimal area. This might reflect both intir advential scarring [10], which would explain the decreasing lumen area in the absence of an i in intimal area.

Pathogenesis

The precise mechanisms for the development of CAV are unclear; but it appears to be multifa A central event leading to the development of CAV appears to be endothelial cell injury [2]. T occur early during organ procurement and reperfusion, both of which can cause ischemia in

endothelial cells. Other factors, such as acute cellular and humoral rejection, hypertension, vi infections, hyperlipidemia, and even immunosuppressive agents [11] can lead eventually to endothelial cell injury, consequent intimal hyperplasia, and the development of CAV (Fig. 1).

Vascular endothelial cell damage causes a cascade of immune responses. These might include coincident upregulation of complement, inflammatory mediators and cytokines [6]. Circulatin antibodies, particularly immunoglobulin G and antibody-antigen complexes, can affect the endothelium further. Platelets can then accumulate on exposed collagen, causing initiation of clotting cascade. Various mediators, including thromboxane, leukotrienes, platelet-derived gr factor, and platelet-activated factors, are released by injured endothelial cells. Subsequently, circulating leukocytes infiltrate tissues by means of the activities of adhesion molecules. Ther loss of the endothelial cell barrier with subsequent lipid accumulation. Multiple signals cause migration of macrophages and smooth muscle cells into the intima of the coronary artery. The transform into foam cells, causing intimal thickening and subsequent vessel lumen obliteratio

Therapy

In general, it can be said that if severe CAV occurs, treatment has not been satisfactory. There emphasis has been placed on prophylaxis. The current prophylaxis options for CAV include modification of risk factors through various medical therapies and strategies. Table 1 lists the areas at which treatment has been targeted. The modification of potential risk factors includes treatment of hypertension, hyperlipidemia, obesity and diabetes, promotion of exercise progra and abstinence from smoking. Although modification of these risk factors in native coronary disease has been found to be beneficial, there is little data to support the efficacy of these mea in preventing CAV. Single-center studies have demonstrated that primary prevention with a s calcium channel blocker or lipid-lowering agent may be beneficial.

Calcium channel blockers

The use of calcium channel blockers was investigated by Schroeder *et al* [12], who randomly 116 heart transplant patients either diltiazem or no calcium channel blocker immediately after transplantation, and assessed these patients with quantitative coronary angiography at 1 and 2 after transplant surgery. The patients treated with diltiazem were less likely to demonstrate a significant decrease in coronary artery luminal diameter in their follow-up angiograms when compared with baseline values. At 5-year follow-up [13], there was a significant difference in freedom from both death and angiographic CAV (56% in the diltiazem group versus 30% in t control group). A major limitation of this study was the use of angiography, since one cannot sufficiently control for variations in vascular tone. In addition, coronary angiography is relati insensitive in detecting early intimal thickening. Mehra *et al* [14] reported on an IVUS study consecutive heart transplant patients who were treated either with a calcium channel blocker, angiotensin-converting enzyme (ACE) inhibitor or a combination of these drugs and compare a control group who did not receive any of these drugs. In the treated groups, therapy was init within 1 month of transplantation as a result of the development of hypertension. At 1-year fo up, coronary artery intimal thickness was significantly greater in the untreated control group t the treated groups.

Cell and animal studies provide supporting evidence that calcium channel blockers may be be in limiting CAV. D'Ambrosio *et al* [15] have demonstrated that diltiazem enhances productio interleukin-1B and slightly reduces production of interleukin-6 in mixed lymphocyte cultures. suggests that diltiazem modulates monokine production and may exert effects on monocytes possibly on other antigen-presenting cells. Finally, Atkinson *et al* [16] reported that the calciu channel blocker amlodipine could significantly decrease narrowing in the coronary arteries of heterotopic transplant model as evaluated by digitized morphometry. Smooth muscle cell mig and proliferation may involve calcium-dependent mechanisms. Calcium channel blockade als

been reported to stabilize endothelial function and inhibit platelet aggregation with a decrease release of platelet-derived growth factors [17]. Therefore, use of calcium channel blockers ma in a decrease in the development of the intimal thickening that characterizes CAV.

Cholesterol lowering agents

Hypercholesterolemia is common after cardiac transplantation, and many studies have associa with the development of CAV [3]. A study at our institution [18] evaluated the use of pravast 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, in primary preven hyperlipidemia in heart transplant recipients. Ninety-seven heart transplant patients were rand to pravastatin or no HMG-CoA reductase inhibitor within 2 weeks of transplant. Twelve mon after transplantation, the pravastatin group had significantly lower mean cholesterol levels tha control group (193 ± 36 versus 248 ± 49 mg/dl), surprisingly less frequent cardiac rejection accompanied by hemodynamic compromise (three versus 14 patients), better survival (94% v 78%), and a lower incidence of CAV as determined both by angiography and autopsy (3 versu patients). In a subgroup of study patients, IVUS measurements at baseline and 1 year after transplantation showed significantly less progression of intimal thickness in the pravastatin gr compared to the control group. In another subgroup of patients, the cytotoxicity of natural kill was significantly lower in the pravastatin group than in the control group (9.8% versus 22.2% specific lysis). This study suggests that the role of pravastatin in decreasing CAV may not onl to cholesterol lowering, but also to an unexpected immunosuppressive effect. Interestingly, th inhibition of natural killer cells by other HMG-CoA reductase inhibitors has been demonstrat *vitro* [19]. Other studies have demonstrated beneficial effects of HMG-CoA reductase inhibit the development of CAV. Wenke *et al* [20] conducted a randomized trial of simvastatin in 72 transplant patients and demonstrated a lower incidence of CAV in simvastatin-treated patients 4 years of this study, CAV was observed in 18% of the simvastatin-treated patients as compar 42% of control patients. In addition, IVUS performed at baseline and at 1-year revealed less progression of intimal thickness in the simvastatin group (170 mm^2 versus 370 mm^2 in the co group).

Pravastatin inhibits the HMG-CoA reductase enzyme and thereby reduces the production of mevalonate. This subsequently lowers cholesterol production and reduces isoprenylation of c proteins such as ras and ras-related proteins. Ras-related proteins play important roles in T cel activation and effector function, which are pivotal in the development of allograft rejection du organ transplantation [21]. These findings of an added immunosuppressive effect of pravastat inhibition of isoprenylation) may in part explain the anti-rejection properties as well as the de development of CAV observed in the pravastatin-treated cardiac transplant patients. In additi inhibition of isoprenylation, there may be other mechanisms by which pravastatin reduces the development of CAV. In a study by Maggard *et al* [22], using a rat model, pravastatin decrea coronary arterial intimal lesions while depressing IgG alloantibody levels, suggesting a role f humoral immune response in the development of CAV, as reported by others [23,24]. Pravast may also have direct vascular effects on intimal proliferation. In another rat study by Maggar [25], pravastatin-treated rats as compared with controls had significantly less degradation of l and fibronectin and had fewer graft-infiltrating macrophages, particularly within the arterial i and perivascular areas. This suggests that the macrophage may also play a major role in the pathogenesis of CAV. The specific mechanisms for these findings in the rat studies are not cl could be related to the inhibition of isoprenylation by pravastatin as previously mentioned.

Other therapies

The somatostatin analog angiopeptin has been demonstrated to have an inhibitory effect on th proliferation of smooth muscle cells in experimental studies [26]. Other experimental data ha shown that angiopeptin inhibits the release of insulin-like growth factor, which may inhibit th proliferation of smooth muscle cells after vascular injury. Wahlers *et al* [27] studied 54 heart

transplant patients who received angiopeptin injections, but found similar survival and angiog coronary atherosclerosis when compared with historical controls.

Photopheresis, a technique that has been in use for several years to treat cutaneous lymphoma (mycosis fungoides), is being investigated as a new therapeutic strategy to modulate the immu response. With photopheresis, patients are given oral 8-methoxy-psoralen and white blood cel subsequently harvested via apheresis techniques. The psoralen-bound white blood cells are th irradiated with ultraviolet light and subsequently re-infused into the patient. It is postulated th treated white blood cells cause a host autoregulatory T cell response, which may have a benef effect on the development of intimal thickness. In a randomized trial by Barr *et al* [28] of 23 c transplant recipients, photopheresis was found to reduce intimal thickening as measured by IV larger multicenter study is currently in progress. Photopheresis may be a promising technique although it is expensive and time-consuming (patients receive photo-pheresis for 4 h during 2 consecutive days; and the procedure is performed at least once monthly for the first year) and therefore may find limited use.

Newer immunosuppressive agents are currently being studied and many have the potential to decrease the development of CAV. In rats with heterotopic heart transplants, recent studies su that treatment with mycophenolate mofetil [29], 15-deoxyspergualin [30], or rapamycin [31] diminish the severity of CAV. The mechanisms of these apparently beneficial effects are not l but appear to reflect more than a decreased incidence of acute rejection. Mycophenolate mofe reportedly blocks purine synthesis and prevents the proliferation of both T lymphocytes and B lymphocytes, therefore blocking both the cellular and humoral responses. A multicenter, doub blind, randomized trial using mycophenolate mofetil versus azathioprine, in combination both cyclosporine and prednisone in 650 heart transplant patients, did not reveal significant differe between groups in the development of CAV by angiography or IVUS at 3 years. However, th number of patients developing CAV was small and therefore more time may be needed to demonstrate differences. Multicenter studies with rapamycin are currently ongoing, with resul CAV becoming available within the next 2 years.

An impaired anticoagulant pathway has been associated with the development of CAV. Aziz colleagues [32] have demonstrated in the rat heterotopic heart model that rats treated with cyclosporine and low-molecular-weight heparin have reduced frequency and severity of CAV as reduced graft rejection. Research interest in antithrombin III has demonstrated the impressi inhibitory activities of these agents in the period after coronary angioplasty. Experience in hea transplant patients has not yet been reported.

Clinical research has also focused on the use of monoclonal antibodies, antimetabolites, and A inhibitors. Monoclonal antibodies target specific growth factors, adhesion molecules, and cyt Future studies using this advanced technology will probably require several monoclonal antib because the etiology of CAV is diverse. Antimetabolites, such as methotrexate, have been use empirically by many transplant physicians to treat patients with CAV. The rationale is to add immuno-suppression with the current belief that CAV is predominantly immune-mediated. H there have been no randomized trials using methotrexate for patients who develop CAV. Mos anecdotal experiences do not show clear benefit. Studies by Mehra *et al* [14,33] have suggest benefit of captopril, an ACE inhibitor, in CAV. In the rat heterotopic heart transplant model, Kobayashi *et al* [34] demonstrated that rats treated with captopril had a lower incidence of cel and vascular rejection, minimal intimal proliferation, and reduced smooth muscle cell prolifer It is suggested that captopril may mediate this vascular response through a paracrine renin-angiotensin mechanism or a suppressive effect on platelet-activating factor. In the DBA/2 to I mouse cardiac allograft model used by Furukawa *et al* [35], which is an MHC compatible combination that differs in background genes only and allows 70% graft survival on day 70 w the use of immunosuppressive drugs, both captopril and the angiotensin II receptor antagonist

116 demonstrated a beneficial effect. Both drugs tended to improve day 70 graft survival and significantly decreased both intimal thickening, and perivascular and interstitial fibrosis, in al grafts. This study suggested that angiotensin II is directly involved in intimal thickening and f and that the beneficial effect of an ACE inhibitor is unrelated to the accumulation of tissue bradykinin activity. Convincing clinical evidence is still lacking to support the routine use of inhibitors in cardiac transplant patients to decrease the development of CAV.

Conclusion

The mechanisms leading to CAV are undoubtedly multiple. They probably involve ischemic that occur at the time of transplantation and both immune and nonimmune factors that occur postoperatively. Endothelial cell injury appears to be central to the pathogenesis of CAV. A multitude of immune responses subsequently occur, leading to smooth muscle cell and macro transformation into foam cells, which results in intimal proliferation and ultimately in obliter the vessel lumen.

Medical therapy to prevent this major complication has progressed slowly. The early use of d and/or pravastatin or simvastatin appears to be the current optimal prophylaxis for decreasing incidence of CAV, but does not completely prevent its development. Multi-center studies wit mycophenolate mofetil, rapamycin, and other newer agents may hold promise for the future. clear that whatever intervention is applied, it must be started at the time of transplantation, as cascade of events determining CAV begins by this time.

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Figures and Tables

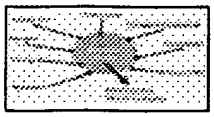

Figure 1
Proposed mechanisms in the development of CAV. Endothelial cell injury has been propc the event that initially triggers proliferation of smooth muscle cells and macrophages (see description).

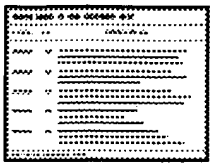

Table 1
Therapeutic modalities to treat cardiac allograft vasculopathy

prophylactic

Dictionary

pro·phy·lac·tic (prō'fə-lăk'tĭk, prŏf'ə-)

adj.

Acting to defend against or prevent something, especially disease; protective.

n.

1. A **prophylactic** agent, device, or measure, such as a vaccine or drug.
2. A contraceptive device, especially a condom.

[French prophylactique, from Greek prophulaktikos, from prophulassein, to take precautions against : pro-, before; see pro-[2] + phulassein, to protect (from phulax, guard).]

prophylactically **pro'phy·lac'ti·cal·ly** *adv.*

▼*Continued below...*

Neurological Glossary

Prophylactic

Treatment given to protect against or ward off disease. Many doctors give antibiotics to patients who have been bitten by ticks as a **prophylactic** measure against Lyme disease.

▼*Continued below...*

Thesaurus

prophylactic

adjective

Defending against disease: preventative, preventive, protective. *See* allow/prevent.

▼*Continued below...*

Medical

pro·phy·lac·tic (prō'fə-lăk'tĭk, prŏf'ə-)
n.

1. A **prophylactic** agent, device, or measure, such as a vaccine or drug.
2. A contraceptive device, especially a condom.

adj.

Acting to defend against or prevent something, especially disease; protective.

▼Continued below...

WordNet

Note: click on a word meaning below to see its connections and related words.

The *noun* **prophylactic** has 2 meanings:

Meaning #1: remedy that prevents or slows the course of an illness or disease
Synonyms: preventive, preventative

Meaning #2: contraceptive device consisting of a thin rubber or latex sheath worn over the penis during intercourse
Synonyms: condom, rubber, safety, safe

The *adjective* **prophylactic** has 3 meanings:

Meaning #1: capable of preventing conception or impregnation
Synonyms: contraceptive, antifertility

Meaning #2: tending to ward off
Synonyms: cautionary, preventive

Meaning #3: preventing or contributing to the prevention of disease
Synonyms: preventive, preventative

Translations

Translations for: Prophylactic

Dansk (Danish)
adj. - forebyggende, præventiv
n. - forebyggende middel, kondom

Nederlands (Dutch)
preventief (geneesmiddel)

Français (French)

adj. - prophylactique
n. - traitement prophylactique, mesure prophylactique

Deutsch (German)
adj. - prophylaktisch, vorbeugend
n. - Prophylaxe, Vorbeugungsmaßnahme

Ελληνική (Greek)
adj. - (ιατρ.) προφυλακτικός
n. - προφυλακτικό (κν. καπότα)

Italiano (Italian)
profilattico

Português (Portuguese)
adj. - profilático
n. - profilático (m)

Русский (Russian)
профилактический, профилактическое средство

Español (Spanish)
adj. - profiláctico, preservativo
n. - profiláctico, preservativo, condón

Svenska (Swedish)
adj. - förebyggande, profylaktisk
n. - skyddsmedel, preventivmedel, förebyggande åtgärd

中文(简体) (Chinese (Simplified))
预防疾病的, 预防药, 避孕药, 预防法

中文(繁體) (Chinese (Traditional))
adj. - 預防疾病的
n. - 預防藥, 避孕藥, 預防法

한국어 (Korean)
adj. - 질병예방의
n. - 예방약, 피임약[용구]

日本語 (Japanese)
n. - 予防薬, 予防法, 予防器具
adj. - 予防する

العربيه (Arabic)
(صفه) وقائي (الاسم) عقار واقي, مانع الحمل

עברית (Hebrew)
adj. - מונע מחלה
n. - אמצעי מניעה, קונדום (צפון-אמריקה)

If you are unable to view some languages clearly, click here.

To select your translation preferences click here.

Heal Digestive Disorders

Mentioned In

prophylactic is mentioned in these AnswerPages:

synteretic	prophylaxis
pyrimethamine	prophylaxis (chess)
Vesicoureteral reflux	therapeutic
Gulf War syndrome	preventive
Proguanil	preventive
	More>

Copyrights:

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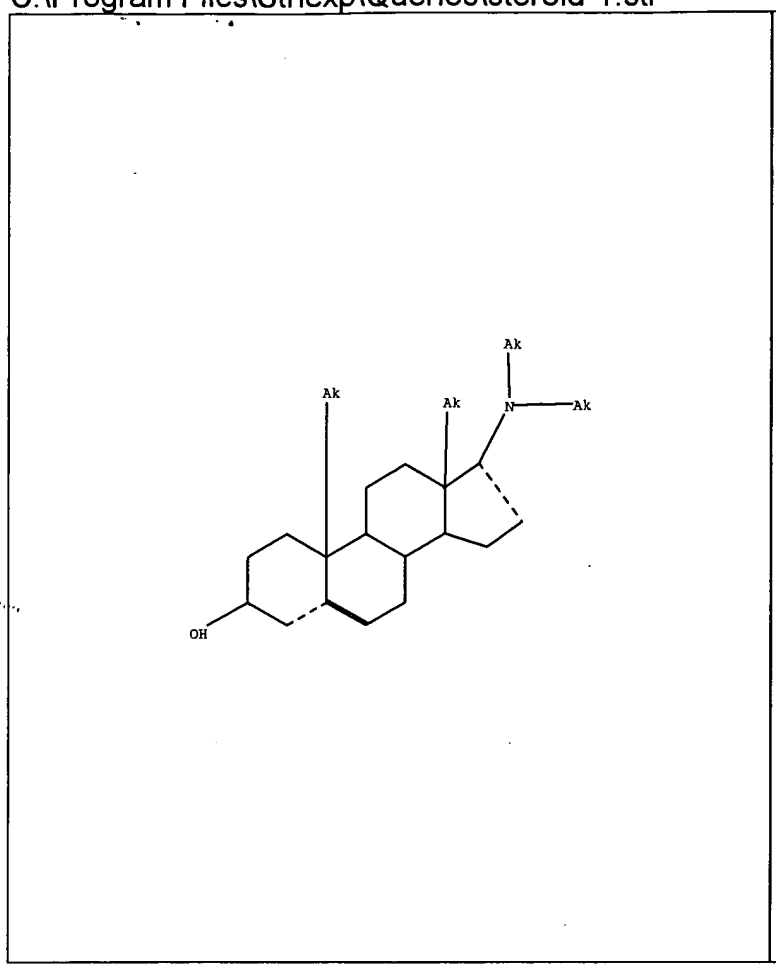

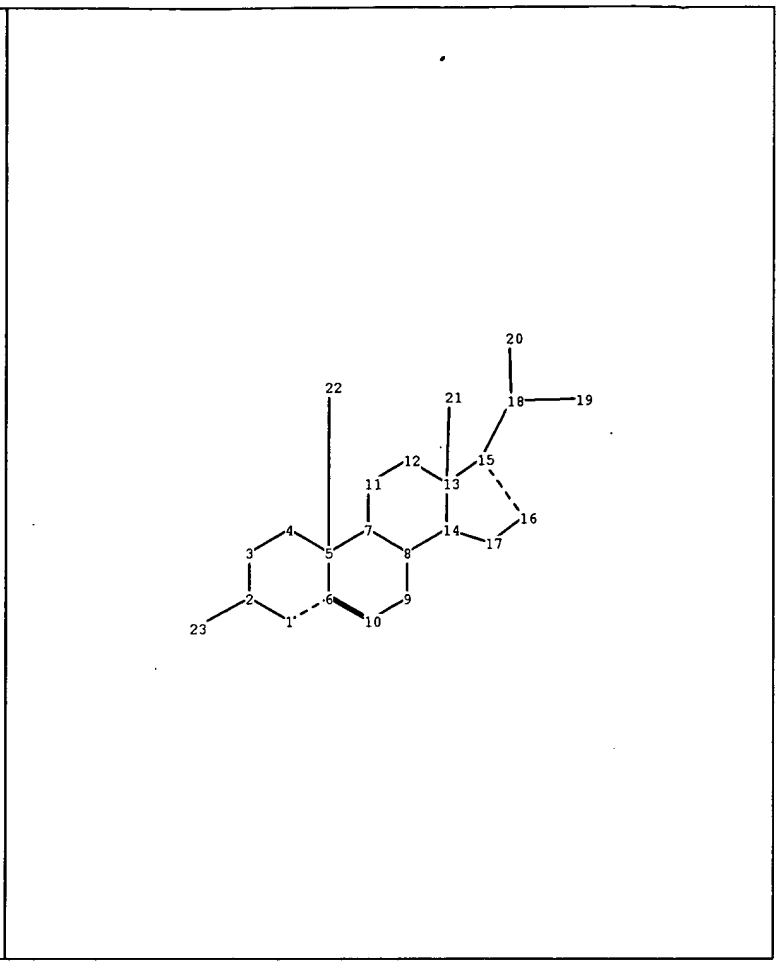

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ring nodes :
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chain bonds :
2-23 5-22 13-21 15-18 18-19 18-20
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-14 9-10 11-12 12-13 13-14 13-15 14-17 15-16 16-17
exact/norm bonds :
1-2 1-6 2-3 2-23 3-4 4-5 5-6 5-7 5-22 6-10 7-8 7-11 8-9 8-14 9-10 11-12 12-13 13-14 13-15 13-21 14-17 15-16 15-18 16-17 18-19 18-20

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS

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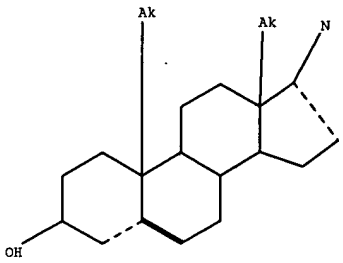
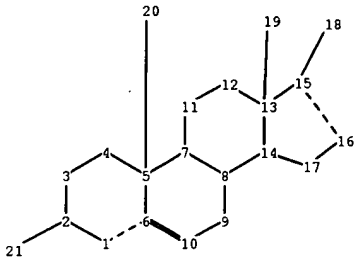




chain nodes :
18 19 20 21
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
chain bonds :
2-21 5-20 13-19 15-18
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-14 9-10 11-12 12-13 13-14 13-15 14-17 15-16 16-17
exact/norm bonds :
1-2 1-6 2-3 2-21 3-4 4-5 5-6 5-7 5-20 6-10 7-8 7-11 8-9 8-14 9-10 11-12 12-13 13-14 13-15 13-19 14-17 15-16 15-18 16-17

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS 20:CLASS 21:CLASS

L35 ANSWER 1 OF 20 USPATFULL on STN
ACCESSION NUMBER: 2004:179017 USPATFULL
TITLE: Therapeutic treatment methods
INVENTOR(S): Reading, Christopher L., San Diego, CA, UNITED STATES
Ahlem, Clarence N., San Diego, CA, UNITED STATES
Auci, Dominick L., San Diego, CA, UNITED STATES
Dowding, Charles, San Diego, CA, UNITED STATES
Frincke, James M., San Diego, CA, UNITED STATES
Li, Mei, San Diego, CA, UNITED STATES
Page, Theodore M., Carlsbad, CA, UNITED STATES
Stickney, Dwight R., Granite Bay, CA, UNITED STATES
Trauger, Richard J., Leucadia, CA, UNITED STATES
White, Steven K., San Diego, CA, UNITED STATES

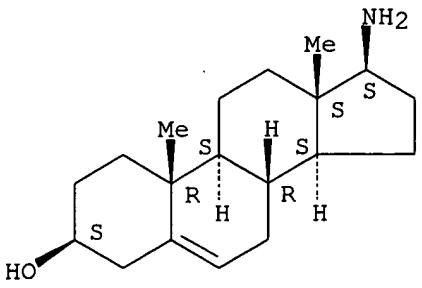
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004138187	A1	20040715	
APPLICATION INFO.:	US 2003-651515	A1	20030828	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-407146P	20020828	(60)
	US 2002-408332P	20020904	(60)
	US 2003-479257P	20030617	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HOLLIS-EDEN PHARMACEUTICALS, INC., 4435 EASTGATE MALL, SUITE 400, SAN DIEGO, CA, 92121
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
LINE COUNT: 16128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of compounds to ameliorate or treat an condition such as a cystic fibrosis, neutropenia or other exemplified conditions. Exemplary compounds that can be used include 3β-hydroxy-17β-aminoandrost-5-ene, 3β-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3α-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3β-hydroxy-16β-fluoro-17β-aminoandrost-5-ene, 1α,3β-dihydroxy-4α-fluoroandrost-5-ene-17-one, 1α,3β,17β-trihydroxy-4α-fluoroandrost-5-ene, 1β,3β-dihydroxy-6α-bromoandrost-5-ene, 1α-fluoro-3β,12α-dihydroxyandrost-5-ene-17-one, 1α-fluoro-3β,4α-dihydroxyandrost-5-ene and 4α-fluoro-3β,6α,17β-trihydroxyandrostane.

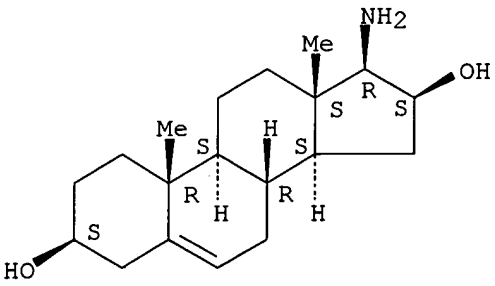
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 4350-66-7 100817-33-2 668987-02-8
668987-03-9 668987-04-0 668987-05-1
668987-06-2
(immunostimulatory methods and compns. with androgen derivs. and other therapeutic uses)
RN 4350-66-7 USPATFULL
CN Androst-5-en-3-ol, 17-amino-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 100817-33-2 USPATFULL
CN Androst-5-ene-3,16-diol, 17-amino-, (3β,16β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 668987-02-8 USPATFULL
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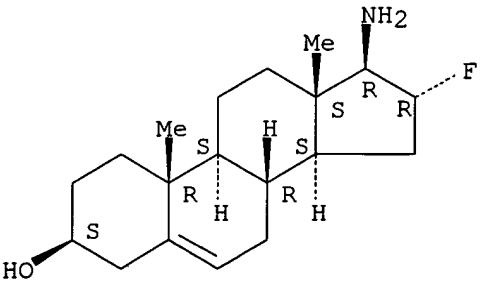
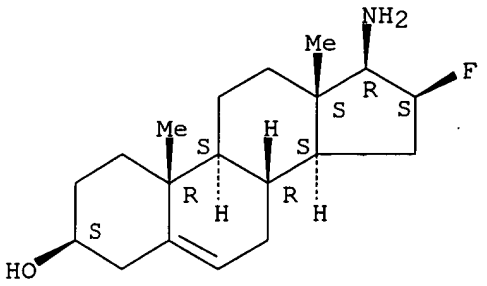
Absolute stereochemistry.



RN 668987-03-9 USPATFULL
CN Androst-5-en-3-ol, 17-amino-16-fluoro-, (3β,16β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 668987-04-0 USPATFULL
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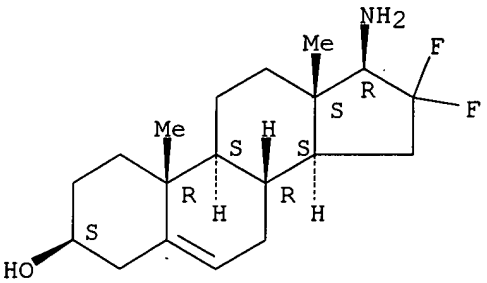
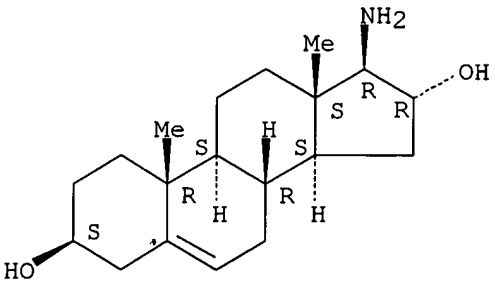
(CA INDEX NAME)

Absolute stereochemistry.



RN 668987-05-1 USPATFULL
CN Androst-5-ene-3,16-diol, 17-amino-, (3β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



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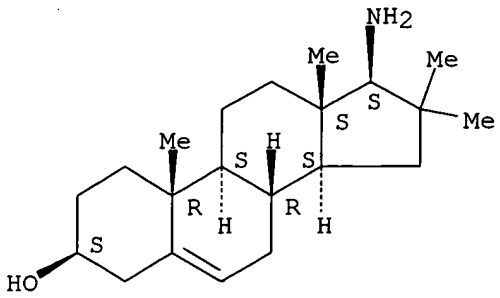
(CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:411062 CAPLUS
DOCUMENT NUMBER: 142:442337
TITLE: Therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation
INVENTOR(S): Reading, Christopher L.; Ahlem, Clarence N.; Auci, Dominick L.; Dowding, Charles; Frincke, James M.; Li, Mei; Page, Theodore M.; Stickney, Dwight R.; Trauger, Richard J.; White, Steven K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 180 pp., Cont.-in-part of U.S. Ser. No. 651,515.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005101581	A1	20050512	US 2003-728400		20031205
US 2004138187	A1	20040715	US 2003-651515		20030828
PRIORITY APPLN. INFO.:			US 2002-407146P	P	20020828
			US 2002-408332P	P	20020904
			US 2003-479257P	P	20030617
			US 2003-651515	A2	20030828

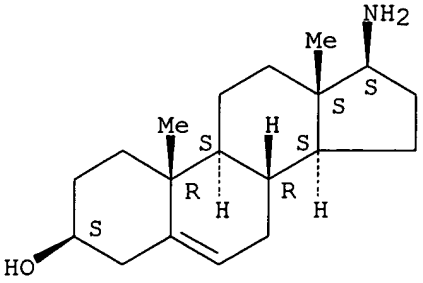
OTHER SOURCE(S): MARPAT 142:442337

AB The invention relates to the use of compds. to ameliorate or treat a condition such as a cystic fibrosis, neutropenia or other exemplified conditions including cardiovascular disease, immune disorders, trauma, and inflammation. Exemplary compds. that can be used include 3β-hydroxy-17β-aminoandrost-5-ene, 3β-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3α-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3β-hydroxy-16β-fluoro-17β-aminoandrost-5-ene, 1α,3β-dihydroxy-4α-fluoroandrost-5-ene-17-one, 1α,3β, 17β-trihydroxy-4α-fluorandrost-5-ene, 1β,3β-dihydroxy-6α-bromoandrost-5-ene, 1α-fluoro-3β,12α-dihydroxyandrost-5-ene-17-one, 1α-fluoro-3β,4α-dihydroxyandrost-5-ene and 4α-fluoro-3β,6α, 17β-trihydroxyandrostane.

IT 4350-66-7 100817-33-2 668987-02-8 668987-03-9 668987-04-0 668987-05-1 668987-06-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
RN 4350-66-7 CAPLUS

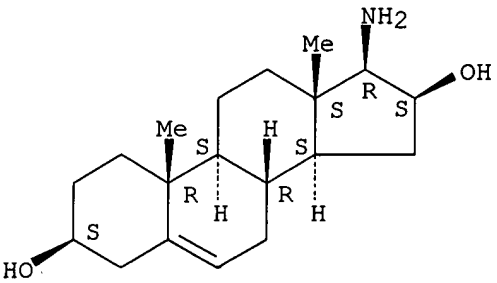
CN Androst-5-en-3-ol, 17-amino-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 100817-33-2 CAPLUS
CN Androst-5-ene-3,16-diol, 17-amino-, (3β,16β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 668987-02-8 CAPLUS
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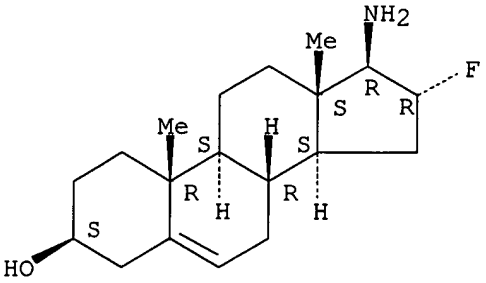
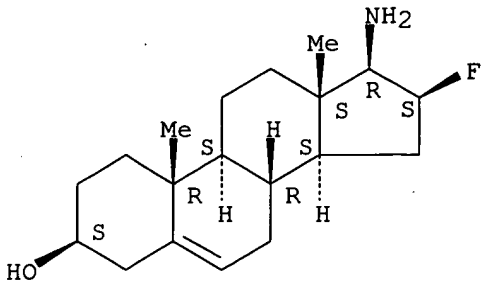
Absolute stereochemistry.



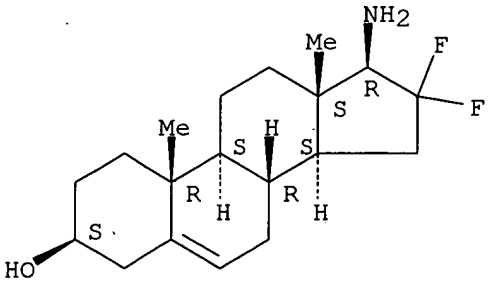
RN 668987-03-9 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16-fluoro-, (3β,16β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 668987-04-0 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-difluoro-, (3β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RN 668987-05-1 CAPLUS
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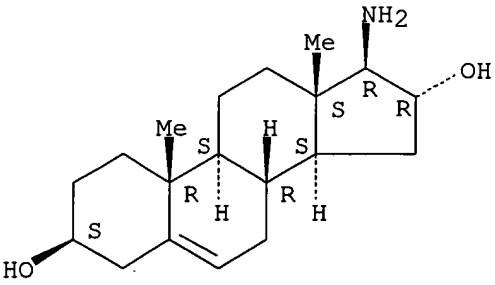
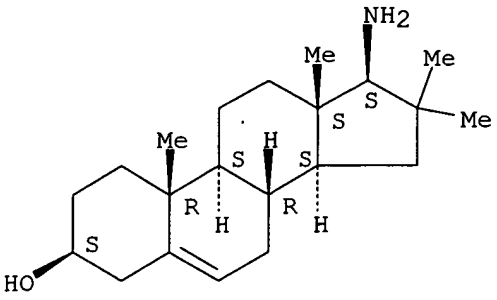
(CA INDEX NAME)

Absolute stereochemistry.



RN 668987-06-2 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-dimethyl-, (3β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:203677 CAPLUS
DOCUMENT NUMBER: 140:229914
TITLE: Immunostimulatory methods and compositions with androgen derivatives and other therapeutic uses
INVENTOR(S): Reading, Christopher; Ahlem, Clarence N.; Auci, Dominick L.; Dowding, Charles; Frincke, James; Li, Mei; Page, Theodore M.; Trauger, Richard J.; Stickney, Dwight R.; White, Steven K.
PATENT ASSIGNEE(S): Hollis-Eden Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 380 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004019953	A1	20040311	WO 2003-US327186		20030828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2496867	AA	20040311	CA 2003-2496867		20030828
AU 2003278744	A1	20040319	AU 2003-278744		20030828
EP 1539183	A1	20050615	EP 2003-770268		20030828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006506445	T2	20060223	JP 2004-569763		20030828
PRIORITY APPLN. INFO.:			US 2002-407146P	P	20020828
			US 2002-408332P	P	20020904
			US 2003-479257P	P	20030617
			WO 2003-US27186	W	20030828

OTHER SOURCE(S): MARPAT 140:229914

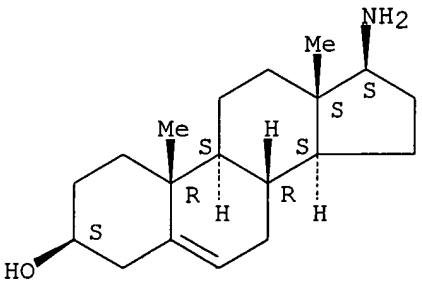
AB The invention relates to the use of compds. to ameliorate or treat conditions such as a cystic fibrosis, neutropenia or other exemplified conditions. Exemplary compds. that can be used include 3β-hydroxy-17β-aminoandrost-5-ene, 3β-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3α-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3β-hydroxy-16β-fluoro-17β-aminoandrost-5-ene, 1α,3β-dihydroxy-4α-fluoroandrost-5-ene-17-one, 1α,3β, 17β-trihydroxy-4α-fluorandrost-5-ene, 1β,3β-dihydroxy-6α-bromoandrost-5-ene,

1α-fluoro-3β,12α-dihydroxyandrost-5-ene-17-one,
1α-fluoro-3β,4α-dihydroxyandrost-5-ene and
4α-fluoro-3β,6α, 17β-trihydroxyandrostante.

IT 4350-66-7 100817-33-2 668987-02-8
668987-03-9 668987-04-0 668987-05-1
668987-06-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory methods and compns. with androgen derivs. and other therapeutic uses)

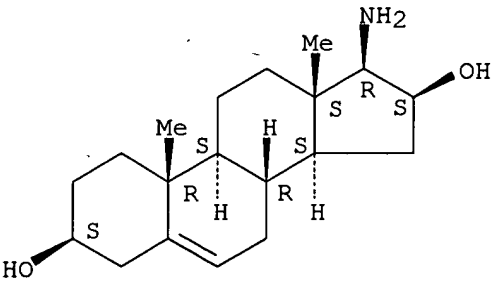
RN 4350-66-7 CAPLUS
CN Androst-5-en-3-ol, 17-amino-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



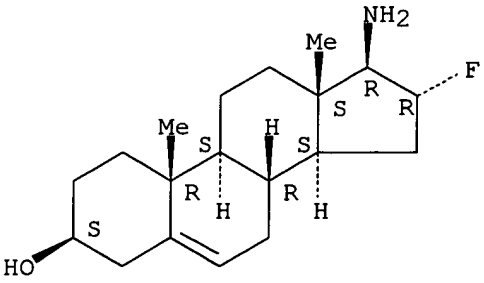
RN 100817-33-2 CAPLUS
CN Androst-5-ene-3,16-diol, 17-amino-, (3β,16β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



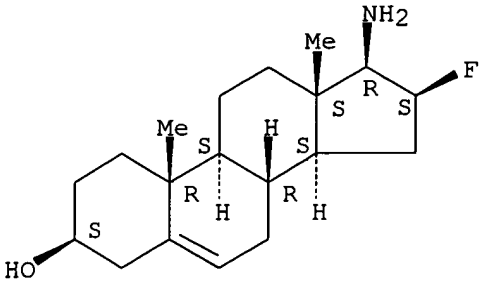
RN 668987-02-8 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16-fluoro-, (3β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



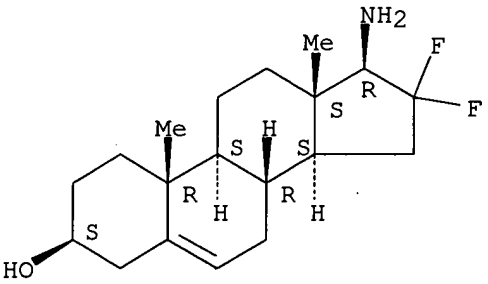
RN 668987-03-9 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16-fluoro-, (3β,16β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



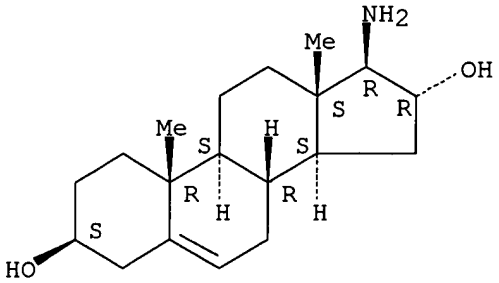
RN 668987-04-0 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-difluoro-, (3β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



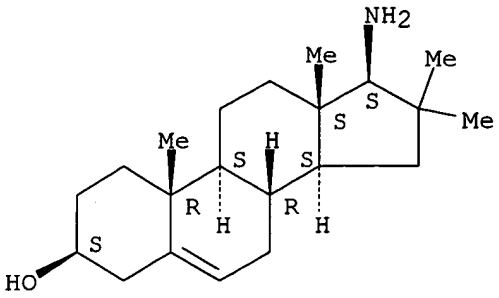
RN 668987-05-1 CAPLUS
CN Androst-5-ene-3,16-diol, 17-amino-, (3β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RN 668987-06-2 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-dimethyl-, (3β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1127711 CAPLUS
DOCUMENT NUMBER: 144:184884
TITLE: Anti-inflammatory and immune regulatory properties of 5-androsten-3β, 17β-diol (HE2100), and synthetic analogue HE3204: implications for treatment of autoimmune diseases
AUTHOR(S): Auci, D.; Nicoletti, F.; Mangano, K.; Pieters, R.; Nierkens, S.; Morgan, L.; Offner, H.; Frincke, J.; Reading, C.
CORPORATE SOURCE: Hollis-Eden Pharmaceuticals, San Diego, CA, USA
SOURCE: Annals of the New York Academy of Sciences (2005), 1051(Autoimmune Diseases and Treatment), 730-742
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

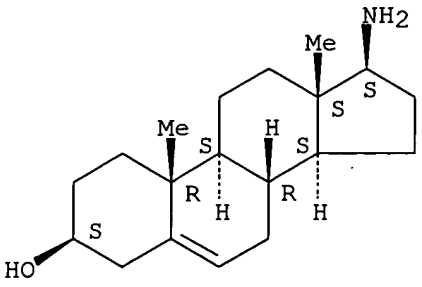
AB 5-Androsten-3β, 17β-diol (HE2100), and a synthetic analog HE3204 are regarded as immune-regulating hormones, because both induce changes in the reporter antigen-popliteal lymph node assay (RA-PLNA). Mice were injected in the footpad with either HE2100 or HE3204 (0.01-3 mg), and a nonsensitizing dose of trinitrophenyl ovalbumin (TNP-OVA) was used as bystander reporter antigen. Seven days later, nodes were removed and nos. of cells (CD3, CD4, CD8, CD19; flow cytometry), TNP-specific IgM, IgG1, and IgG2a antibody-forming cells (AFCs; ELISPOT assay), and cytokines (interleukin-4 [IL-4], interferon-γ [IFN-γ]; ELISA) were measured. HE2100 and HE3204 increased cell nos. in a dose-dependent fashion. T (helper and suppressor) cells and B cells were increased (>5-fold). HE3204 was apparently twice as potent as HE2100. Both increased the B/T ratio (fivefold), increased TNP-specific IgM and IgG1 (.apprx.50-fold), and induced IgG2a AFCs. Both increased IL-4 and IFN-γ secretion (up to threefold). Both displayed anti-inflammatory activity in the murine model of carrageenan-induced pleurisy, as evidenced by reduced neutrophil nos. and exudate vols. Our observations suggest that both HE2100 and HE3204 are immune-regulating steroid hormones that exhibit anti-inflammatory properties. HE2100 (1 mg/mouse per day) provided significant benefit when given at disease onset in the SJL/J female mouse model of exptl. autoimmune encephalomyelitis. These compds. and their analogs are candidates for further testing in autoimmune diseases.

IT 4350-66-7
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HE3204 had greater anti-inflammatory activity than HE2100 in carrageenan-induced pleurisy by reducing neutrophil and exudate volume and HE2100 reduced lethality during LPS-induced shock and provided benefit from EAE in mouse)

RN 4350-66-7 CAPLUS

CN Androst-5-en-3-ol, 17-amino-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:472466 CAPLUS
DOCUMENT NUMBER: 135:97440
TITLE: Preparation and use of a drug composition containing local anesthetics, anti-inflammatory agent and/or immunostimulant
INVENTOR(S): Kasch, Helmut; Goldschmidt, Carsten
PATENT ASSIGNEE(S): ID Pharma G.m.b.H., Germany
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045678	A2	20010628	WO 2000-EP13036	20001220
WO 2001045678	A3	20020411		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001031620	A5	20010703	AU 2001-31620	20001220
PRIORITY APPLN. INFO.:			DE 1999-19961834 A	19991221
			WO 2000-EP13036 W	20001220

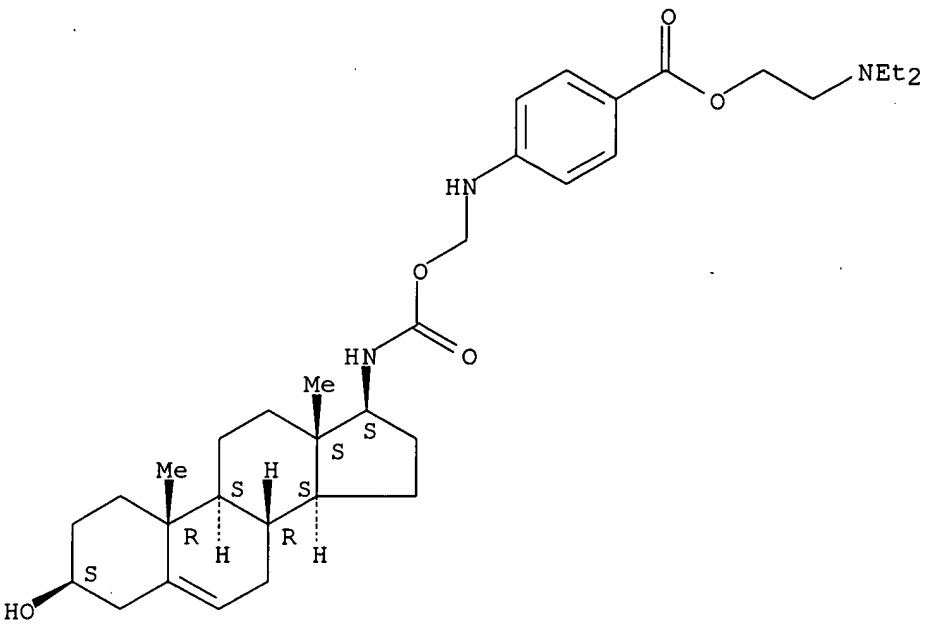
OTHER SOURCE(S): MARPAT 135:97440

AB The invention relates to a composition which comprises as its constituents (a) a local anesthetic and (b) an anti-inflammatory compound and/or an immunostimulant compound and/or a compound which acts as a supporting material for the local anesthetic. The components can be linked via a chemical bond forming carbamates or thiocarbamates. The compns. are use for the treatment of autoimmune diseases, inflammations, neurol. diseases, asthma, age-related diseases etc. Thus PAR 1 was prepared by reacting PAR 2 with procaine hydrochloride in methylene chloride for 2 h at room temperature The product was chromatographed on silica gel and identified by ESI-MS. Its was used to screen various microorganisms; PAR 1 inhibited the growth of Penicillium notatum, Glomerella cingulata and Kluyveromyces marxianus.

IT 346707-08-2 346707-09-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and use of a drug composition containing local anesthetics, anti-inflammatory agent and/or immunostimulant)

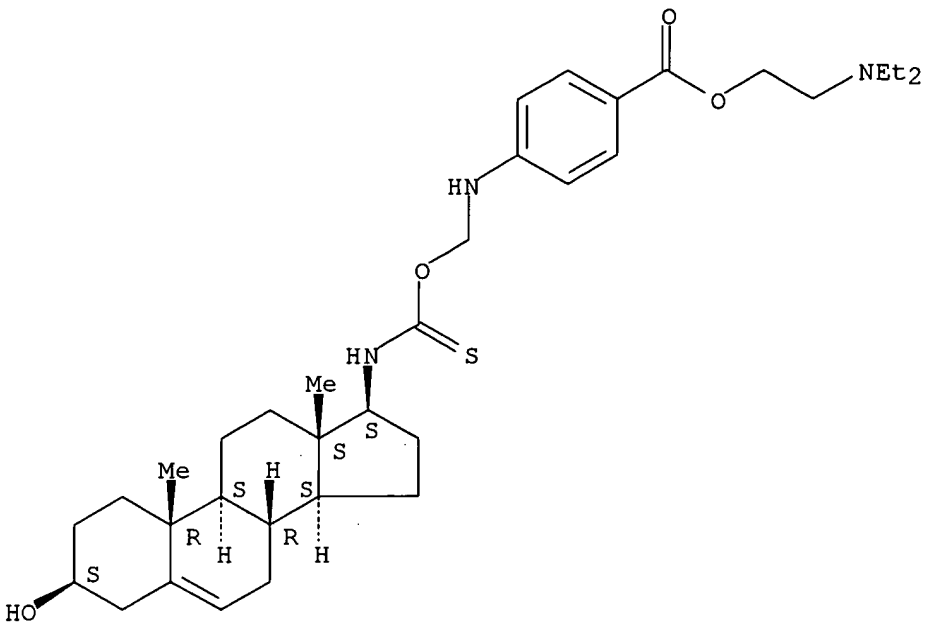
RN 346707-08-2 CAPLUS
CN Benzoic acid, 4-[[[[[[(3β,17β)-3-hydroxyandrost-5-en-17-yl]amino]carbonyl]oxy]methyl]amino]-, 2-(diethylamino)ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 346707-09-3 CAPLUS
CN Benzoic acid, 4-[[[[[[(3β,17β)-3-hydroxyandrost-5-en-17-yl]amino]thioxomethoxy]methyl]amino]-, 2-(diethylamino)ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:175443 CAPLUS
DOCUMENT NUMBER: 140:403738
TITLE: Effectiveness of 20,25-diazacholesterol, avian gonadotropin-releasing hormone, and chicken riboflavin carrier protein for inhibiting reproduction in Coturnix quail
AUTHOR(S): Yoder, C. A.; Andelt, W. F.; Miller, L. A.; Johnston, J. J.; Goodall, M. J.
CORPORATE SOURCE: National Wildlife Research Center, Fort Collins, CO, 80521-2154, USA
SOURCE: Poultry Science (2004), 83(2), 234-244
CODEN: POSCAL; ISSN: 0032-5791
PUBLISHER: Poultry Science Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Contraception may provide a useful nonlethal management tool when it is desirable to reduce populations of birds. The authors tested the efficacy of 20,25-diazacholesterol, and immunization with avian gonadotropin-releasing hormone (AGnRH-I) and chicken riboflavin carrier protein (cRCP) as contraceptives and investigated their modes of action in Coturnix quail (Coturnix coturnix japonica). Females that were paired with males treated with 20,25-diazacholesterol produced lower percentages of eggs that were fertile and hatched. Females treated with 20,25-diazacholesterol and paired with control males laid fewer eggs, and lower percentages of their eggs were fertile and hatched. Treatment with 20,25-diazacholesterol reduced testosterone levels in males and progesterone levels in females. Nonesterified cholesterol levels were reduced, whereas desmosterol levels increased in birds treated with 20,25-diazacholesterol. Treatment with AGnRH-I and cRCP immunocontraceptive vaccines did not decrease average egg production and hatchability or hormone levels, but this failure might have been due to the vaccination protocol. If registered, wildlife managers may be able to use 20,25-diazacholesterol when other methods, such as lethal control, are undesirable for reducing damage caused by specific breeding behaviors such as the building of nests.

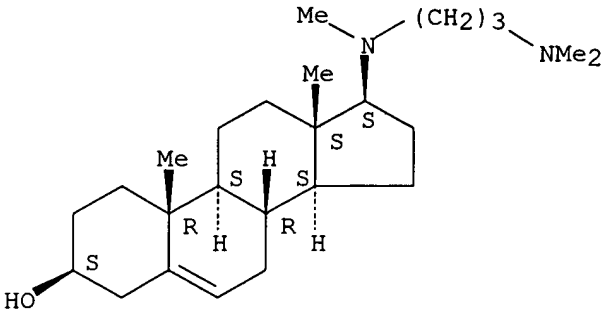
IT 313-05-3, 20,25-Diazacholesterol
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(diazacholesterol and avian gonadotropin-releasing hormone and chicken riboflavin carrier protein for inhibition of reproduction in Japanese quail Coturnix coturnix japonica)

RN 313-05-3 CAPLUS

CN Androst-5-en-3-ol, 17-[[3-(dimethylamino)propyl]methylamino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:136529 CAPLUS

DOCUMENT NUMBER: 142:212406

TITLE: Method for treating cachexia with RXR retinoid ligands

INVENTOR(S): Jiang, Guang Liang; Yuan, Yang-Dar; Chandraratna, Roshantha A.

PATENT ASSIGNEE(S): Allergan, Inc., USA

SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005013949	A2	20050217	WO 2004-US25564	20040806
WO 2005013949	A3	20050915		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004263156	A1	20050217	AU 2004-263156	20040806
CA 2535260	AA	20050217	CA 2004-2535260	20040806
EP 1653939	A2	20060510	EP 2004-780406	20040806
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				

PRIORITY APPLN. INFO.:

US 2003-493138P	P	20030807
US 2003-533734P	P	20031231
WO 2004-US25564	W	20040806

OTHER SOURCE(S): MARPAT 142:212406

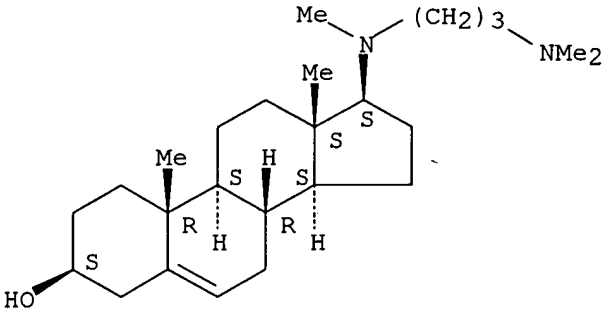
AB The invention discloses a method for the treatment of cachexia in a subject in need of treatment. More specifically, the invention discloses the use of retinoid compds. that act on retinoid X receptors (RXRs) for the treatment of cachexia in a subject in need of treatment. The cachexia is associated with a complication of a primary disease, condition or disorder. Primary diseases, conditions and disorders include, but are not limited to, cancer, AIDS, liver cirrhosis, diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, chronic cardiac failure, immune system diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus), tuberculosis, cystic fibrosis, gastrointestinal disorders (e.g., irritable bowel syndrome and inflammatory bowel disease), Parkinson's disease, anorexia nervosa, dementia, major depression, an aged condition, and sarcopenia.

IT 313-05-3, Azacosterol
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RXR retinoid ligands for cachexia treatment)

RN 313-05-3 CAPLUS

CN Androst-5-en-3-ol, 17-[[3-(dimethylamino)propyl]methylamino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:400277 CAPLUS

DOCUMENT NUMBER: 117:277

TITLE: Mechanism of allergic cross-reactions. I. Multispecific binding of ligands to a mouse monoclonal anti-DNP IgE antibody

AUTHOR(S): Varga, Janos M.; Kalchschmid, Gertrud; Klein, Georg F.; Fritsch, Peter

CORPORATE SOURCE: Dep. Dermatol., Univ. Innsbruck, Innsbruck, 6020, Austria

SOURCE: Molecular Immunology (1991), 28(6), 641-54
CODEN: MOIMD5; ISSN: 0161-5890

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A recently developed solid-phase binding assay was used to investigate the specificity of ligand binding to a mouse monoclonal anti-dinitrophenyl IgE (I). All DNP-amino acids, that were tested inhibited the binding of the radio-labeled I to DNP covalently attached to polystyrene microplates; however, the concentration for 50% inhibition varied within four orders of magnitude, DNP-L-serine being the most and DNP-L-proline the least potent inhibitor. In addition to DNP analogs, a large number of drugs and other compds. were tested for their ability to compete with DNP for the binding site of I. At the concentration used for screening, 59% of compds. had no significant inhibition; 19% inhibited the binding of I more than 50%. Several families of compds. (tetracyclines, polymyxins, phenothiazines,

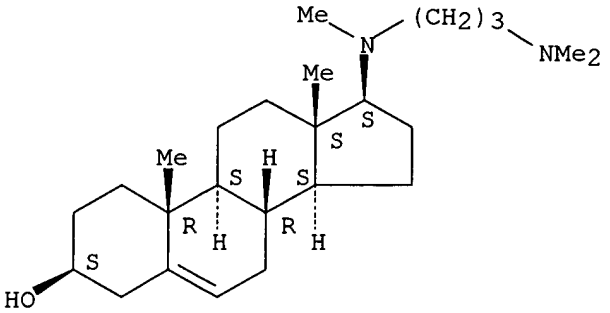
salicylates, and quinones) that were effective competitors were found. Within these families, changes in the functional groups attached to the family stem had major effects on the affinity of ligand binding. The occurrence frequencies of interactions of ligands with I is in good agreement with the semi-empirical model for multispecific antibody-ligand interactions.

IT 1249-84-9, Azacosterol.hydrochloride
RL: BIOL (Biological study)
(binding of, to anti-dinitrophenol monoclonal antibody, allergic cross-reaction mechanisms in relation to)

RN 1249-84-9 CAPLUS

CN Androst-5-en-3-ol, 17-[[3-(dimethylamino)propyl]methylamino]-, dihydrochloride, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

L35 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1970:20295 CAPLUS

DOCUMENT NUMBER: 72:20295

TITLE: Effect of hypocholesteremic agents on an experimental brain tumor in mice

AUTHOR(S): Grossi Paoletti, Enrica; Sirtori, C. R.; Weiss, J. F.; Paoletti, R.

CORPORATE SOURCE: Inst. Pharmacol., Univ. Milan, Milan, Italy

SOURCE: Advan. Exp. Med. Biol. (1969), Volume 4, 457-71. Editor(s): Holmes, William L. Plenum Press: New York, N. Y.
CODEN: AEMBAP

DOCUMENT TYPE: Conference

LANGUAGE: English

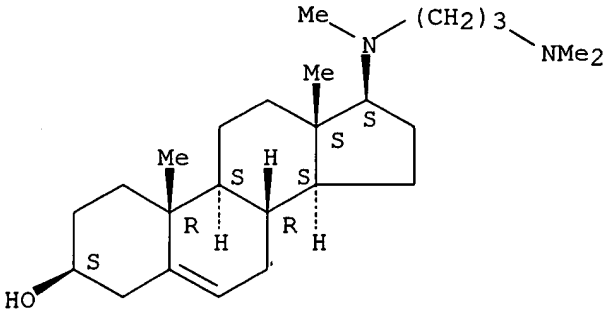
AB A series of compds. interfering with cholesterol biosynthesis and transport were tested against a transplantable ependymoma of the mouse. The antimitotic agent, vincristine, was also used for comparison. AY-9944 administered in the diet was an effective inhibitor of tumor growth and the possibility of an additive effect of a combined treatment with AY-9944 and vincristine is indicated. Triparanol, injected s.c., also inhibited tumor growth. These drugs drastically altered the sterol pattern of plasma and tumor. The possible correlations between effects on tumor growth and changes in plasma and tumor sterols are discussed.

IT 313-05-3
RL: BIOL (Biological study)
(neoplasms of brain in response to)

RN 313-05-3 CAPLUS

CN Androst-5-en-3-ol, 17-[[3-(dimethylamino)propyl]methylamino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

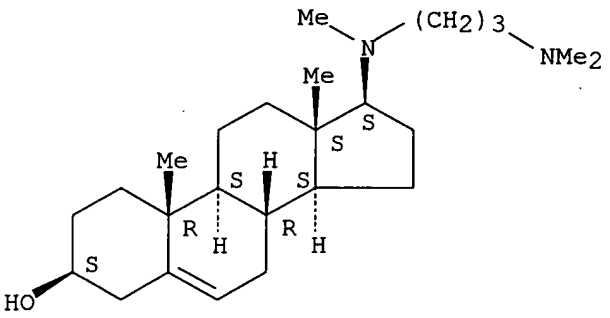


L35 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:146549 CAPLUS
DOCUMENT NUMBER: 104:146549
TITLE: Fast to slow transition induced by experimental myotonia in rat EDL muscle
AUTHOR(S): Salviati, G.; Biasia, E.; Betto, R.; Betto, D. Danieli
CORPORATE SOURCE: Cent. Stud. Biol. Fisiopatol. Muscolare, Ist. Patol. Gen., Padua, I-35100, Italy
SOURCE: Pfluegers Archiv (1986), 406(3), 266-72
CODEN: PFLABK; ISSN: 0031-6768
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exptl. myotonia was induced by feeding rats with 20,25-diazacholesterol for up to 8 mo. Histochem. anal. of myotonic extensor digitorum longus (EDL) muscle showed a progressive decrease of type IIB fibers and a concomitant increase of IIA and type I fibers. A transient hypertrophy of type IIA fibers was observed 6 mo after beginning the treatment. Anal. of the pattern of myosin light chains of single fibers from EDL showed that myotonia caused a progressive decrease of fibers showing a pure fast myosin light chain pattern and an increase of fibers showing coexistence of fast and slow myosin light chains (intermediate fibers). Only a small percentage of intermediate fibers showed coexistence of fast and slow myosin heavy chains. Myotonic fibers presented an increased sensitivity to caffeine which approached that of normal soleus fibers. Furthermore, sarcoplasmic reticulum (SR) vesicles isolated from hind limb fast muscles of myotonic rats demonstrated a decrease of Ca2+-dependent ATPase and Ca2+-transport activities as well as a decrease of immunoreactivity with anti-rabbit SR fast Ca2+-ATPase antibody. Apparently, the increased elec. activity brought about by 20,25-diazacholesterol-induced myotonia, caused a fast to slow transition in the phenotypic expression of myosin and sarcoplasmic reticulum proteins.

IT 313-05-3
RL: BIOL (Biological study)
(myotonia from, myosins and sarcoplasmic reticulum proteins and muscle fiber types in)
RN 313-05-3 CAPLUS
CN Androst-5-en-3-ol, 17-[[3-(dimethylamino)propyl]methylamino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 11 OF 20 USPATFULL on STN

ACCESSION NUMBER:	94:109016 USPATFULL
TITLE:	Steroid compounds
INVENTOR(S):	Johnson, Roy A., Kalamazoo, MI, United States Bundy, Gordon L., Portage, MI, United States Youngdale, Gilbert A., Portage, MI, United States Morton, Douglas R., Portage, MI, United States Wallach, deceased, Donald P., late of Richland, MI, United States by Vera M. Wallach, legal representative
PATENT ASSIGNEE(S):	The Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5373095		19941213
APPLICATION INFO.:	US 1993-126153		19930923 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1992-972693, filed on 6 Nov 1992, now patented, Pat. No. US 5274089 which is a division of Ser. No. US 1991-793486, filed on 13 Nov 1991, now patented, Pat. No. US 5187299 which is a continuation of Ser. No. US 1991-657729, filed on 20 Feb 1991, now abandoned which is a division of Ser. No. US 1989-394396, filed on 15 Aug 1989, now abandoned which is a division of Ser. No. US 1987-117851, filed on 16 Jun 1987, now patented, Pat. No. US 4917826 which is a continuation-in-part of Ser. No. US 1986-843120, filed on 24 Mar 1986, now abandoned which is a continuation-in-part of Ser. No. US 1985-788995, filed on 8 Oct 1985, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Richter, Johann
ASSISTANT EXAMINER:	Cook, Rebecca
LEGAL REPRESENTATIVE:	Wootton, Thomas A.
NUMBER OF CLAIMS:	2
EXEMPLARY CLAIM:	1
LINE COUNT:	4711

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are cyclic hydrocarbons of Formula I ##STR1## with an aminoalkyl sidechain that are useful for treating phospholipase A2 mediated conditions, diabetes, and obesity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

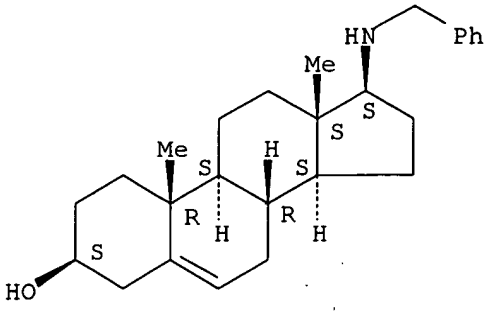
IT 2640-80-4P 112648-10-9P 112648-13-2P
112648-17-6P 112648-21-2P 112648-23-4P
112648-24-5P 112710-69-7P
(preparation of, as phospholipase A2 inhibitor and/or antidiabetic agent)

RN 2640-80-4 USPATFULL

CN Androst-5-en-3-ol, 17-[(phenylmethyl)amino]-, (3β,17β)- (9CI)

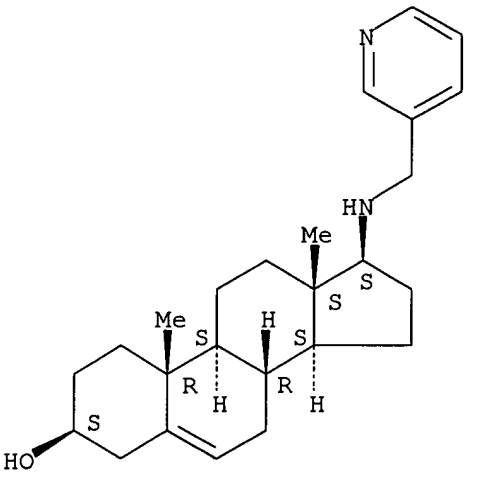
(CA INDEX NAME)

Absolute stereochemistry.



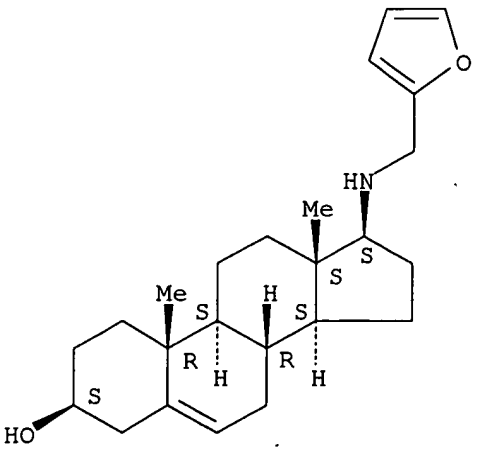
RN 112648-10-9 USPATFULL
CN Androst-5-en-3-ol, 17-[(3-pyridinylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



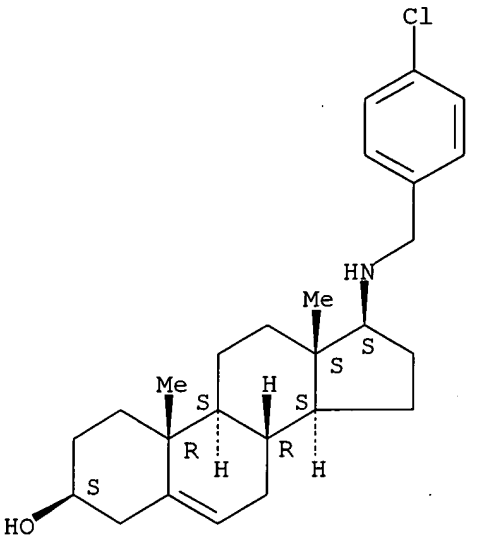
RN 112648-13-2 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-furanylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



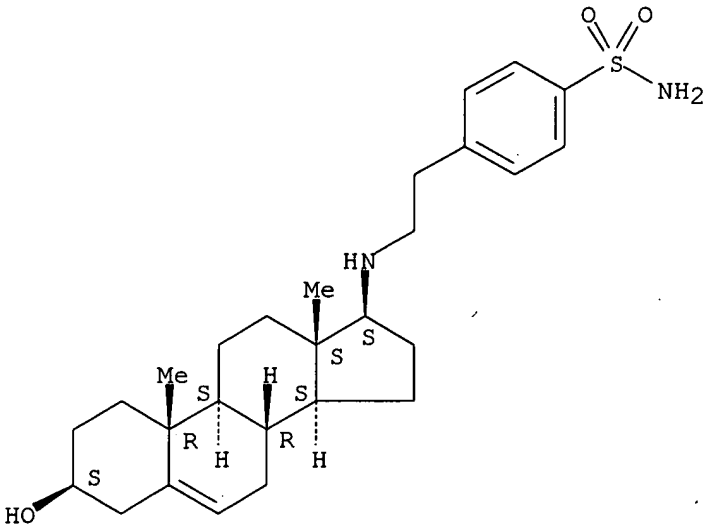
RN 112648-17-6 USPATFULL
CN Androst-5-en-3-ol, 17-[[(4-chlorophenyl)methyl]amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



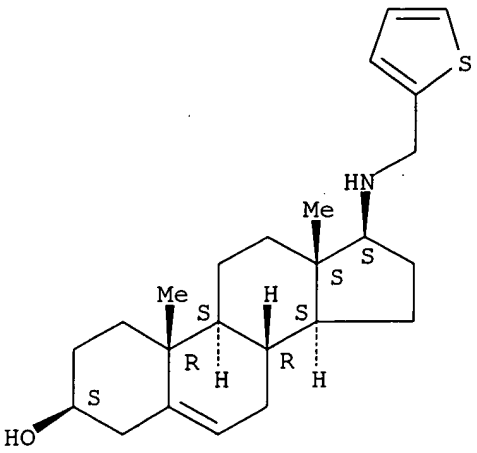
RN 112648-21-2 USPATFULL
CN Benzenesulfonamide, 4-[2-[[(3β,17β)-3-hydroxyandrost-5-en-17-yl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



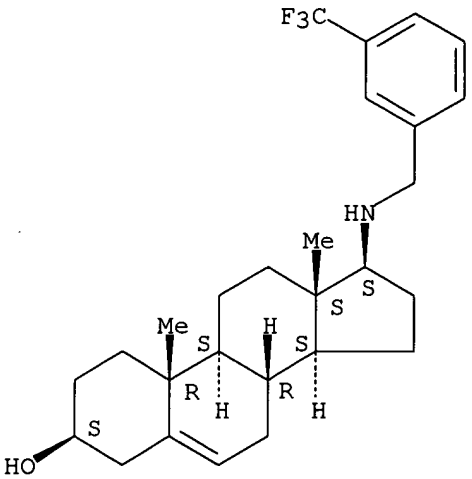
RN 112648-23-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-thienylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



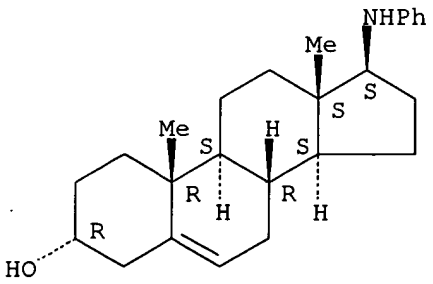
RN 112648-24-5 USPATFULL
CN Androst-5-en-3-ol, 17-[[[3-(trifluoromethyl)phenyl]methyl]amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 112710-69-7 USPATFULL
CN Androst-5-en-3-ol, 17-(phenylamino)-, (3α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 12 OF 20 USPATFULL on STN

ACCESSION NUMBER: 94:66602 USPATFULL
TITLE: Cyclic hydrocarbons with an aminoalkyl sidechain
INVENTOR(S): Johnson, Roy A., Kalamazoo, MI, United States
Bundy, Gordon L., Portage, MI, United States
Youngdale, Gilbert A., Portage, MI, United States
Morton, Douglas R., Portage, MI, United States
Wallach, deceased, Donald P., late of Richland, MI, United States by Vera M. Wallach, Legal Representative
PATENT ASSIGNEE(S): The Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)

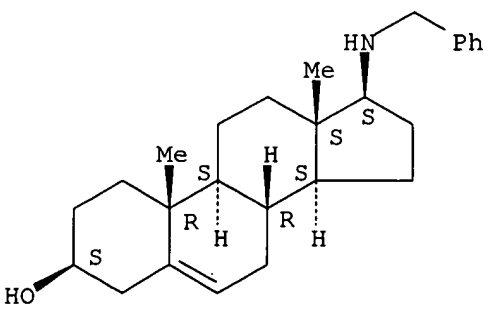
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5334712		19940802
APPLICATION INFO.:	US 1992-976751		19921116 (7)

RELATED APPLN. INFO.: Division of Ser. No. US 1991-657721, filed on 20 Feb 1991, now patented, Pat. No. US 5196524, issued on 23 Mar 1993 which is a division of Ser. No. US 1989-394396, filed on 15 Aug 1989, now abandoned which is a division of Ser. No. US 1987-117851, filed on 16 Jun 1987, now patented, Pat. No. US 4917826 which is a continuation-in-part of Ser. No. US 1986-843120, filed on 24 Mar 1986, now abandoned which is a continuation-in-part of Ser. No. US 1985-788995, filed on 18 Oct 1985, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shahl, Mukund J.
ASSISTANT EXAMINER: Sripada, P. K.
LEGAL REPRESENTATIVE: Wootton, Thomas A.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 4587
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are cyclic hydrocarbons of Formula I ##STR1## with an aminoalkyl sidechain that are useful for treating phospholipase A2 mediated conditions, diabetes, and obesity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 2640-80-4P 112648-10-9P 112648-13-2P
112648-17-6P 112648-21-2P 112648-23-4P
112648-24-5P 112710-69-7P
(preparation of, as phospholipase A2 inhibitor and/or antidiabetic agent)
RN 2640-80-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(phenylmethyl)amino]-, (3β,17β)- (9CI)
(CA INDEX NAME)

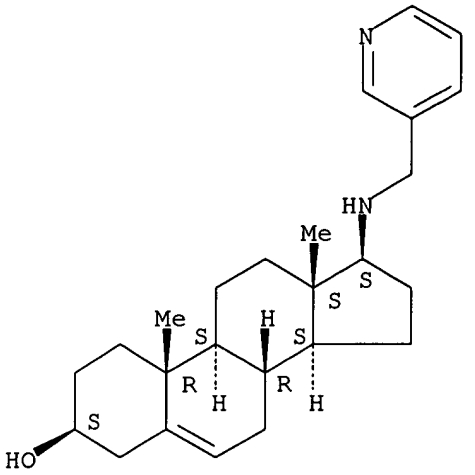
Absolute stereochemistry.



RN 112648-10-9 USPATFULL

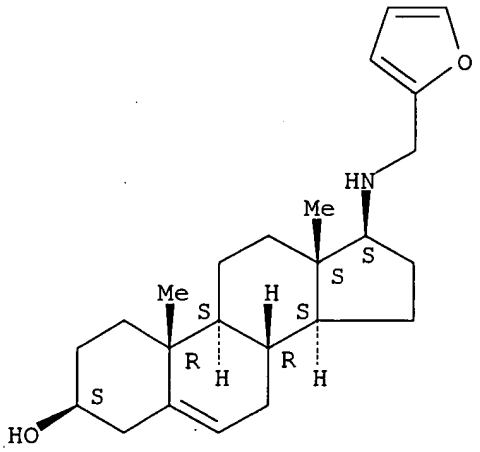
CN Androst-5-en-3-ol, 17-[(3-pyridinylmethyl)amino]-, (3β,17β)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



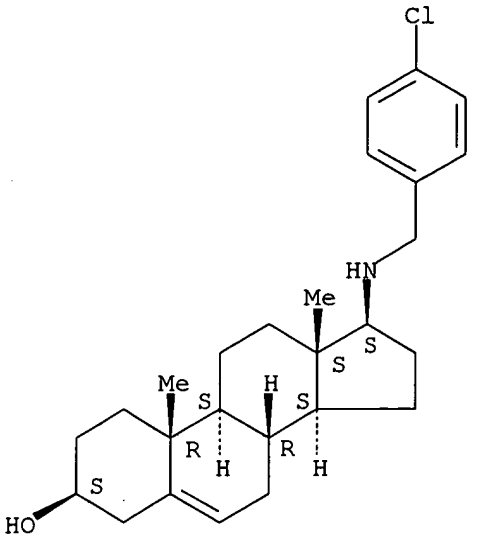
RN 112648-13-2 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-furanylmethyl)amino]-, (3β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



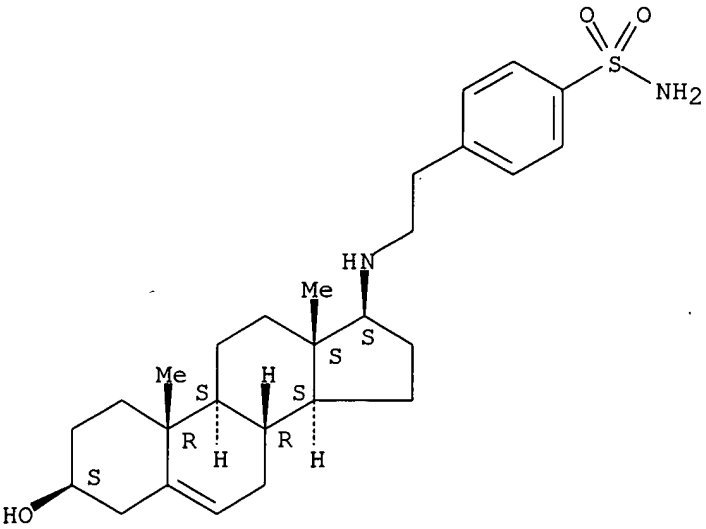
RN 112648-17-6 USPATFULL
CN Androst-5-en-3-ol, 17-[[(4-chlorophenyl)methyl]amino]-,
(3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



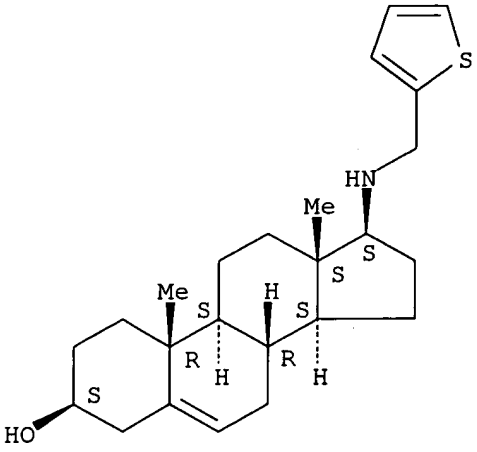
RN 112648-21-2 USPATFULL
CN Benzenesulfonamide, 4-[2-[[(3β,17β)-3-hydroxyandrost-5-en-17-yl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



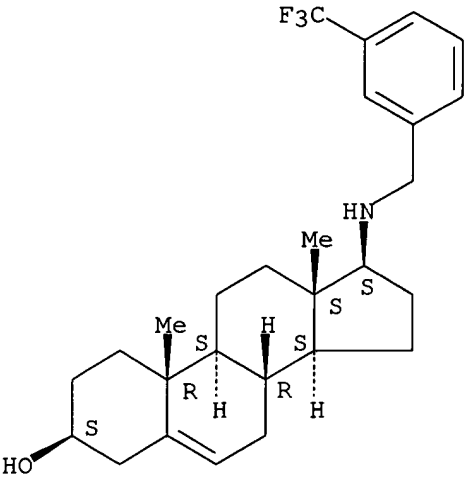
RN 112648-23-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-thienylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



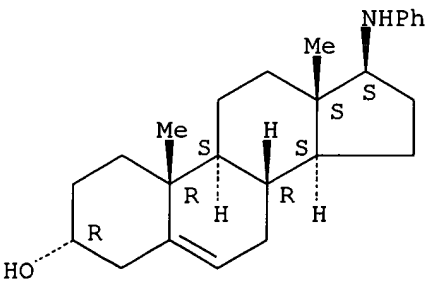
RN 112648-24-5 USPATFULL
CN Androst-5-en-3-ol, 17-[[[3-(trifluoromethyl)phenyl]methyl]amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 112710-69-7 USPATFULL
CN Androst-5-en-3-ol, 17-(phenylamino)-, (3α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 13 OF 20 USPATFULL on STN

ACCESSION NUMBER: 93:109187 USPATFULL
TITLE: Cyclic hydrocarbons with an aminoalkyl sidechain
INVENTOR(S): Bundy, Gordon L., Kalamazoo, MI, United States
Wallach, deceased, Donald P., late of Richland, MI, United States by Vera M. Wallach, legal representative
PATENT ASSIGNEE(S): The Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)

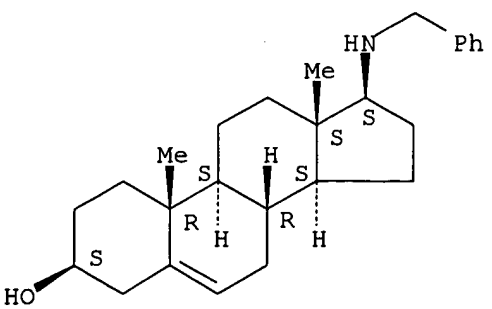
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5274089		19931228
APPLICATION INFO.:	US 1992-972693		19921106 (7)

RELATED APPLN. INFO.: Division of Ser. No. US 1991-793486, filed on 13 Nov 1991, now patented, Pat. No. US 5187299 which is a continuation of Ser. No. US 1991-657729, filed on 20 Feb 1991, now abandoned which is a division of Ser. No. US 1989-394396, filed on 15 Aug 1989, now abandoned which is a division of Ser. No. US 1987-117851, filed on 16 Jun 1987, now patented, Pat. No. US 4917826 which is a continuation of Ser. No. US 1986-102116, filed on 7 Oct 1986, now abandoned which is a continuation-in-part of Ser. No. US 1986-843120, filed on 24 Mar 1986, now abandoned which is a continuation-in-part of Ser. No. US 1985-788995, filed on 18 Oct 1985, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cintins, Marianne M.
ASSISTANT EXAMINER: Kestler, Kimberly J.
LEGAL REPRESENTATIVE: Wootton, Thomas A.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 4555
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are cyclic hydrocarbons of Formula I ##STR1## with an aminoalkyl sidechain that are useful for treating phospholipase A2 mediated conditions, diabetes, and obesity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 2640-80-4P 112648-10-9P 112648-13-2P
112648-17-6P 112648-21-2P 112648-23-4P
112648-24-5P 112710-69-7P
(preparation of, as phospholipase A2 inhibitor and/or antidiabetic agent)
RN 2640-80-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(phenylmethyl)amino]-, (3β,17β)- (9CI)
(CA INDEX NAME)

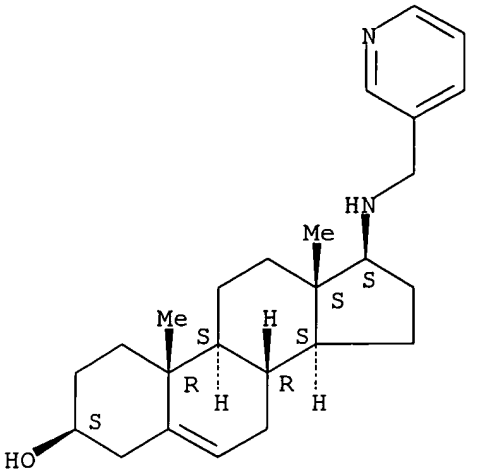
Absolute stereochemistry.



RN 112648-10-9 USPATFULL

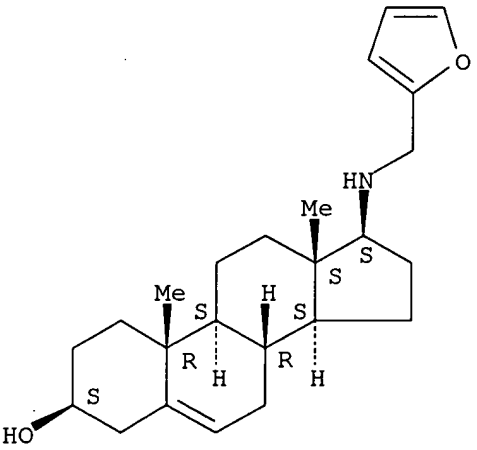
CN Androst-5-en-3-ol, 17-[(3-pyridinylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



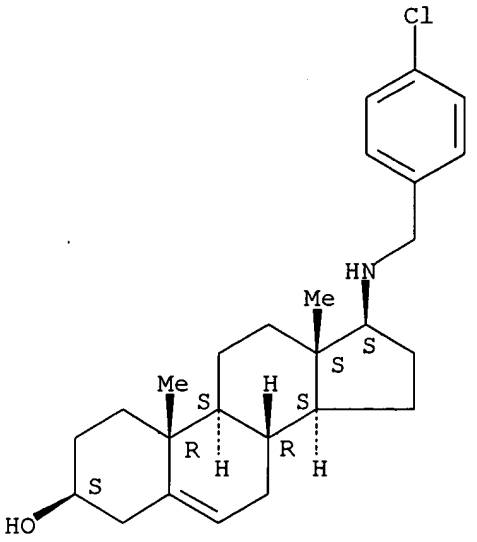
RN 112648-13-2 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-furanylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



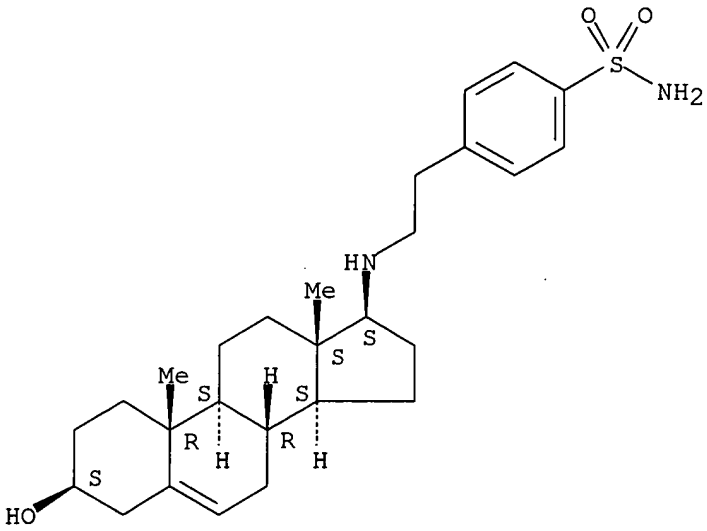
RN 112648-17-6 USPATFULL
CN Androst-5-en-3-ol, 17-[[(4-chlorophenyl)methyl]amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



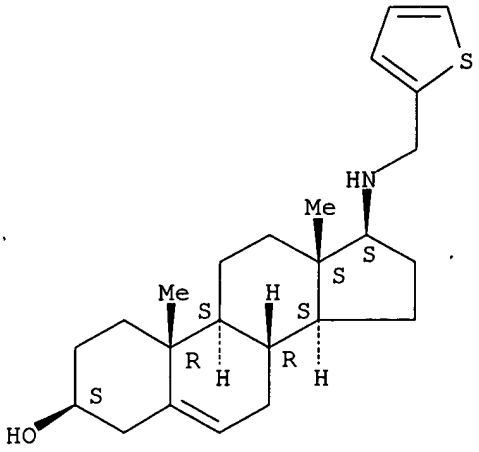
RN 112648-21-2 USPATFULL
CN Benzenesulfonamide, 4-[2-[[(3β,17β)-3-hydroxyandrost-5-en-17-yl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



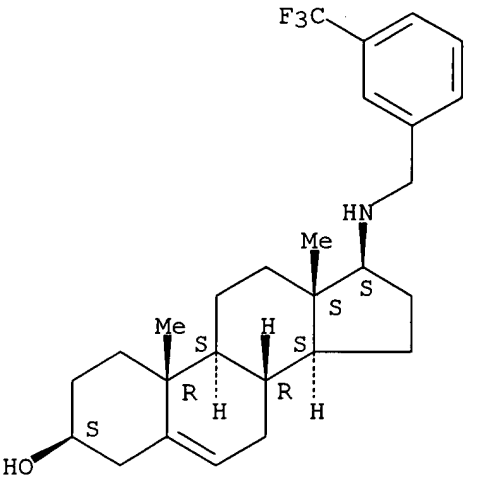
RN 112648-23-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-thienylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



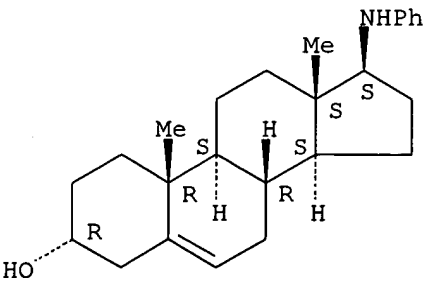
RN 112648-24-5 USPATFULL
CN Androst-5-en-3-ol, 17-[[[3-(trifluoromethyl)phenyl]methyl]amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 112710-69-7 USPATFULL
CN Androst-5-en-3-ol, 17-(phenylamino)-, (3α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 14 OF 20 USPATFULL on STN

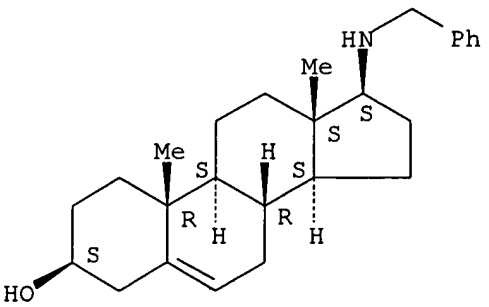
ACCESSION NUMBER: 93:22826 USPATFULL
TITLE: Cyclic hydrocarbons with an aminoalkyl sidechain
INVENTOR(S): Johnson, Roy A., Kalamazoo, MI, United States
Bundy, Gordon L., Portage, MI, United States
Youngdale, Gilbert A., Portage, MI, United States
Morton, Douglas R., Portage, MI, United States
Wallach, deceased, Donald P., late of Richland, MI, United States by Vera M. Wallach, legal representative
PATENT ASSIGNEE(S): The Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5196542		19930323
APPLICATION INFO.:	US 1991-657721		19910220 (7)

RELATED APPLN. INFO.: Division of Ser. No. US 1989-394396, filed on 15 Aug 1989 which is a division of Ser. No. US 1987-117851, filed on 16 Jun 1987, now patented, Pat. No. US 4917826 which is a continuation-in-part of Ser. No. US 1986-843120, filed on 24 Mar 1986, now abandoned which is a continuation-in-part of Ser. No. US 1985-788995, filed on 18 Oct 1985, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Bond, Robert T.
LEGAL REPRESENTATIVE: Wright, Debbie K., Wootton, Thomas A.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 4544
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are cyclic hydrocarbons of Formula I ##STR1## with an aminoalkyl sidechain that are useful for treating phospholipase A2 mediated conditions, diabetes, and obesity.

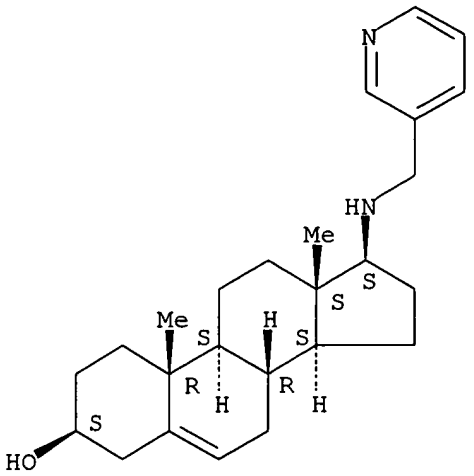
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 2640-80-4P 112648-10-9P 112648-13-2P
112648-17-6P 112648-21-2P 112648-23-4P
112648-24-5P 112710-69-7P
(preparation of, as phospholipase A2 inhibitor and/or antidiabetic agent)
RN 2640-80-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(phenylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



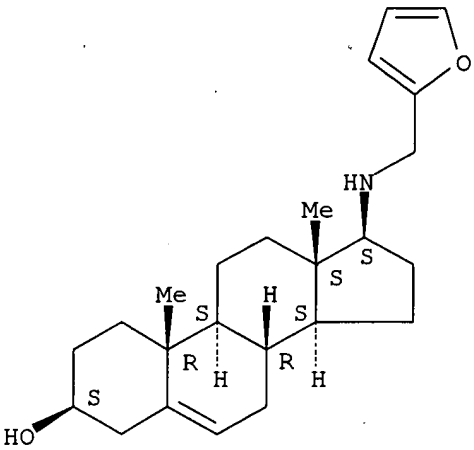
RN 112648-10-9 USPATFULL
CN Androst-5-en-3-ol, 17-[(3-pyridinylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



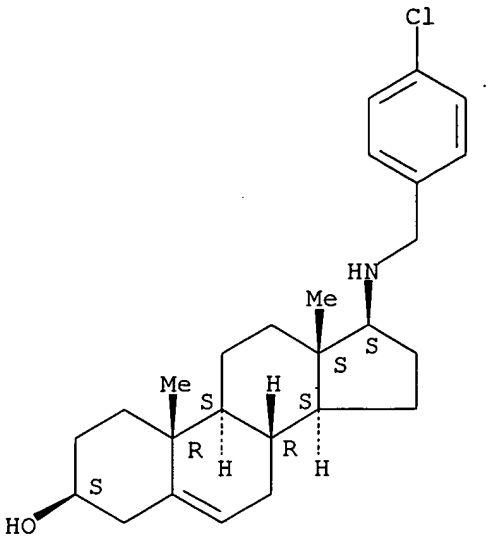
RN 112648-13-2 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-furanylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



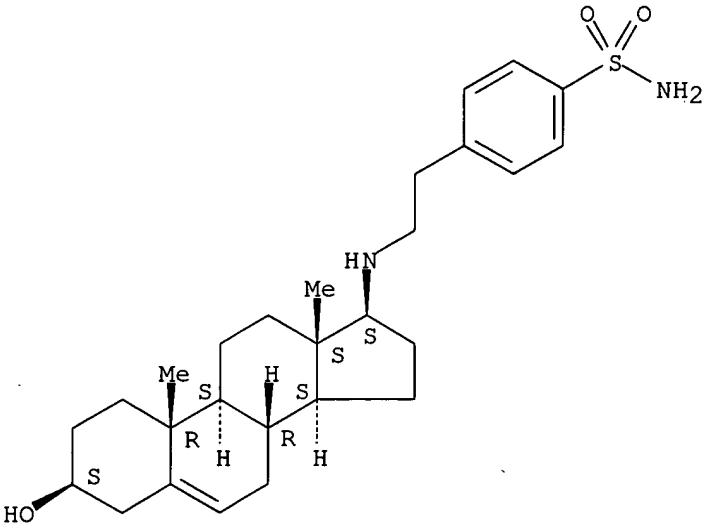
RN 112648-17-6 USPATFULL
CN Androst-5-en-3-ol, 17-[[(4-chlorophenyl)methyl]amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 112648-21-2 USPATFULL
CN Benzenesulfonamide, 4-[2-[[(3β,17β)-3-hydroxyandrost-5-en-17-yl]amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 112648-23-4 USPATFULL
CN Androst-5-en-3-ol, 17-[(2-thienylmethyl)amino]-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:411062 CAPLUS
DOCUMENT NUMBER: 142:442337
TITLE: Therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation
INVENTOR(S): Reading, Christopher L.; Ahlem, Clarence N.; Auci, Dominick L.; Dowding, Charles; Frincke, James M.; Li, Mei; Page, Theodore M.; Stickney, Dwight R.; Trauger, Richard J.; White, Steven K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 180 pp., Cont.-in-part of U.S. Ser. No. 651,515.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
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PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
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US 2004138187	A1	20040715	US 2003-651515		20030828
PRIORITY APPLN. INFO.:			US 2002-407146P	P	20020828
			US 2002-408332P	P	20020904
			US 2003-479257P	P	20030617
			US 2003-651515	A2	20030828

OTHER SOURCE(S): MARPAT 142:442337

AB The invention relates to the use of compds. to ameliorate or treat a condition such as a cystic fibrosis, neutropenia or other exemplified conditions including cardiovascular disease, immune disorders, trauma, and inflammation. Exemplary compds. that can be used include 3β-hydroxy-17β-aminoandrost-5-ene, 3β-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3α-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3β-hydroxy-16β-fluoro-17β-aminoandrost-5-ene, 1α,3β-dihydroxy-4α-fluoroandrost-5-ene-17-one, 1α,3β, 17β-trihydroxy-4α-fluorandrost-5-ene, 1β,3β-dihydroxy-6α-bromoandrost-5-ene, 1α-fluoro-3β,12α-dihydroxyandrost-5-ene-17-one, 1α-fluoro-3β,4α-dihydroxyandrost-5-ene and 4α-fluoro-3β,6α, 17β-trihydroxyandrostane.

IT Immunosuppressants
Immunosuppression
Ionizing radiation
(-induced immune disorder; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Glucocorticoids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-induced immunosuppression; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Aging, animal
Antiviral agents
Chemotherapy
Radiation
Transplant and Transplantation
(-induced neutropenia; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Infection
(-related symptoms; therapeutic use of androgens for various conditions

including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AP-1 (activator protein 1), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ATF-3 (activating transcription factor 3), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT DNA microarray technology
(Affymetrix 417-418 form, gene expression profiles in response to therapeutic agents; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C/EBP-β (CCAAT box/enhancer element-binding protein β), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD54, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Inflammation
(Crohn's disease; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Intestine, disease
(Crohn's; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Cul1, TNFAIP6, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ECP (eosinophil cationic protein), abnormal elevation, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Egr-1, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABP (GA-binding protein), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GATA-3, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Macrophage inflammatory protein 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(GRO-2, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-1 (intercellular adhesion mol. 1), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interleukin receptors
Interleukins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IL-23, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Antibodies and Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IgE, reduction of; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IκB (inhibitor of NF-κB), Kb, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IκB-α (NF-κB inhibitor α), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Blood vessel, disease
(Kawasaki; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NF-κB (nuclear factor of κ light chain gene enhancer in B-cells), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NFKB1 (nuclear factor of κ light chain gene enhancer in B-cells, 1), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT1 (signal transducer and activator of transcription 1), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT3 (signal transducer and activator of transcription 3), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT4 (signal transducer and activator of transcription 4), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT5 (signal transducer and activator of transcription 5), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT5A (signal transducer and activator of transcription 5A), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT5B (signal transducer and activator of transcription 5B), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT6 (signal transducer and activator of transcription 6), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TBX21 (T-box 21), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TSG-6, xCT, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(USF1 (upstream stimulatory factor 1), therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Eosinophil
Macrophage
Neutrophil
(abnormal elevation, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interleukin 8
RANTES (chemokine)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(abnormal elevation, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant and Transplantation
(allotransplant, unwanted immune response; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant rejection
(allotransplant; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Antiarteriosclerotics
(antiatherosclerotics; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Lung, disease
(atelectasis, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Allergy
(atopy; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Mental and behavioral disorders
(autism; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Transplant and Transplantation
(bone marrow; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Bronchi, disease
Inflammation
(bronchiolitis, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-fos, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-jun, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Burn
(chemical; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Disease, animal
(cyanosis, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Leukotrienes
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cysteine-containing, abnormal elevation, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Nerve, disease
(degeneration, therapeutic effects on; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Allergy
(delayed hypersensitivity, modulation of; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Androgens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Mucous membrane
(disease, plugging, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Platelet (blood)
(disease, thrombocytopenia; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Breathing (animal)

(dyspnea, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Lung, disease
(edema, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcriptional regulation
(effect of therapeutic agents on; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Lung, disease
(failure, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Bone, disease
(fracture; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Pain
(from vascular occlusion; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Artery, disease
(giant cell arteritis; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant and Transplantation
(graft-vs.-host reaction; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant and Transplantation
(heart; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Immune disease
(immunosenescence; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Gene expression profiles, animal
(in response to therapeutic agents; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Sweat
(increased chloride concns., infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Lung, disease
(increased vascular permeability, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Brain, disease
(infarction; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Hepatitis B virus
Hepatitis C virus
Human immunodeficiency virus 1
Human immunodeficiency virus 2
Simian immunodeficiency virus
(infection-related immunosuppression; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Burkholderia

Haemophilus influenzae
Pseudomonas
Staphylococcus
Staphylococcus aureus
(infection-related symptoms; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Cough
(infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Lung, disease
Respiratory system, disease
(infection; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Intestine, disease
(inflammatory; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Pancreas, disease
(insufficiency, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Chemokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interferon γ-inducible protein-10, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(junB, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant and Transplantation
(kidney; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant and Transplantation
(liver; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transplant and Transplantation
(lung; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(macrophage-activating factor, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Fertility disorders
(male, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Hematopoiesis
(modulation, therapeutic effects on; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Behavior
(motor, therapeutic effects on; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Disease, animal
(mucous membrane, plugging, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease,

immune disorders, trauma, and inflammation)

IT Agranulocytosis
(neutropenia; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Blood vessel, disease
(occlusion, pain from; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Cyclin dependent kinase inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21CIP1, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interleukin 12
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p35 and p40, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p50, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Artery, disease
Inflammation
(periarteritis nodosa; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Pleura, disease
(pneumothorax, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Edema
(pulmonary, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Hypertension
Infection
(pulmonary; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Connective tissue, disease
(scleroderma; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Inflammation
Respiratory system, disease
(sinusitis, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Bronchi, disease
(spasm, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Lupus erythematosus
(systemic; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Glucocorticoid antagonists
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic agents as; therapeutic use of androgens for various

conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Central nervous system
Ischemia
Learning
Memory, biological
(therapeutic effects on; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Drug delivery systems
(therapeutic formulations; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT Allergy
Allergy inhibitors
Analgesics
Anti-inflammatory agents
Anti-ischemic agents
Antiarteriosclerotics
Anticholesteremic agents
Antihypertensives
Antirheumatic agents
Arteriosclerosis
Atherosclerosis
Autoimmune disease
Burn
Cardiovascular agents
Cardiovascular system, disease
Cystic fibrosis
Hemorrhage
Human
Hypercholesterolemia
Hypertension
Hypertriglyceridemia
Hypolipemic agents
Immunostimulants
Immunostimulation
Inflammation
Lupus erythematosus
Multiple sclerosis
Osteoarthritis
Primates
Rheumatoid arthritis
Sickle cell anemia
Transplant rejection
(therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)
IT C-reactive protein
FcαRI receptors
Interleukin 10
Interleukin 12 receptors
Interleukin 1α
Interleukin 1β
Interleukin 4
Interleukin 6
Lymphotoxin
Macrophage inflammatory protein 1α
Macrophage inflammatory protein 2
Macrophage inflammatory protein 2β
Monocyte chemoattractant protein-1
Thioredoxins
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Phagocytosis
(therapy-stimulated; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Blood, disease
(thrombocytopenia; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Bone marrow
Heart
Kidney
Liver
Lung
(transplant; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Injury
(trauma; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Blood vessel, disease
(vasiculitis; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Breathing (animal)
(wheezing, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interleukin 2 receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α chain, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interferons
Lymphotoxin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β1-, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT Interferon receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ-interferon, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 50-02-2, Dexamethasone 50-18-0, Cyclophosphamide 50-23-7, Cortisol
51-21-8, 5-Fluorouracil 53-03-2, Prednisone 7440-06-4D, Platinum,

compds. 15663-27-1, Cisplatin 41575-94-4, Carboplatin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-induced immunosuppression; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 9059-22-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(1, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 9054-89-1, Superoxide dismutase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2, therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 9004-06-2, Neutrophil elastase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(abnormal elevation, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 7585-39-9D, β-Cyclodextrin, sulfobutyl ethers
RL: RGT (Reagent); RACT (Reactant or reagent)
(in pharmaceutical formulation; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(intolerance, infection-related; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 12619-70-4, Cyclodextrin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of formulation; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 63-05-8, Androst-4-ene-3,17-dione 521-17-5 566-19-8 571-20-0
571-36-8, Androst-5-ene-3,17-dione 897-06-3, Androsta-1,4-diene-3,17-dione 1159-67-7 1649-27-0 1852-53-5 2695-06-9 2697-85-0
4350-66-7 10459-09-3 10459-27-5 14167-49-8 14167-52-3 14339-58-3
19316-59-7 27261-27-4 28507-02-0 41238-32-8 41469-93-6
63230-55-7 66791-83-1 80724-81-8 80724-82-9 100817-33-2
104194-83-4 112859-71-9 147781-66-6 409080-93-9 409080-94-0
502849-05-0 515159-77-0 515159-78-1
515159-81-6 515159-82-7 515159-83-8
515159-84-9 668986-06-9 668986-07-0
668986-08-1 668986-09-2 668986-10-5
668986-11-6 668986-12-7 668986-13-8
668986-14-9 668986-15-0 668986-16-1
668986-17-2 668986-18-3 668986-19-4
668986-20-7 668986-21-8 668986-22-9
668986-23-0 668986-24-1 668986-25-2
668986-26-3 668986-27-4 668986-28-5
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(F1, F48)
F33-34
F45 F37-F49

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668987-08-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

IT 9001-12-1, MMP-1 9032-20-6, NADPH:quinone oxidoreductase 50812-37-8, Glutathione S-transferase 79955-99-0, MMP-3 152478-57-4 153190-61-5, Tyk2 kinase 212906-83-7, Protein kinase RIP2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(therapy-modulated levels; therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation)

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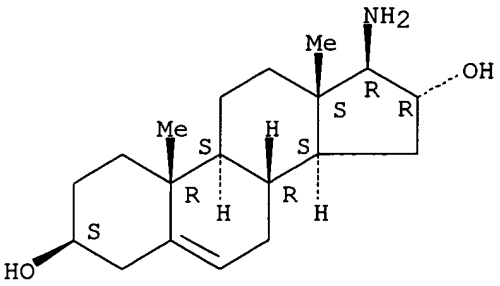
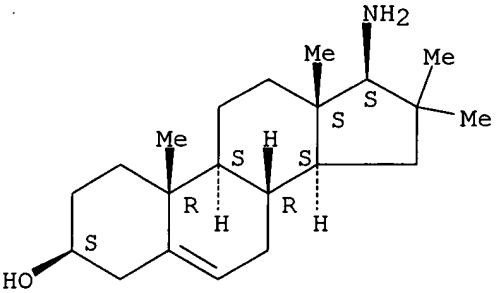


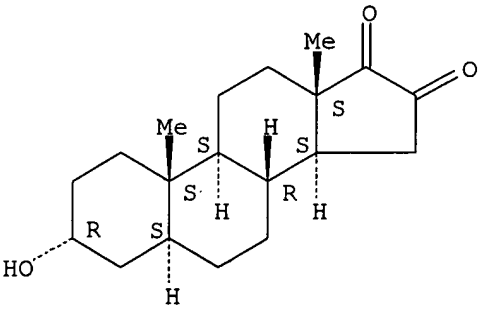
RN 668987-06-2 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-dimethyl-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



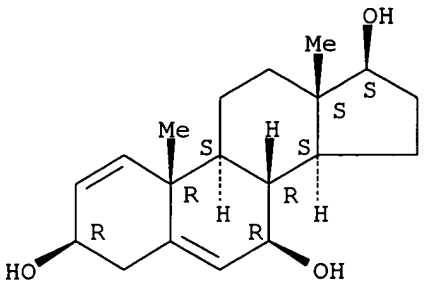
RN 668987-07-3 CAPLUS
CN Androstane-16,17-dione, 3-hydroxy-, (3α,5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 668987-08-4 CAPLUS
CN Androsta-1,5-diene-3,7,17-triol, (3β,7β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:203677 CAPLUS
DOCUMENT NUMBER: 140:229914
TITLE: Immunostimulatory methods and compositions with androgen derivatives and other therapeutic uses
INVENTOR(S): Reading, Christopher; Ahlem, Clarence N.; Auci, Dominick L.; Dowding, Charles; Frincke, James; Li, Mei; Page, Theodore M.; Trauger, Richard J.; Stickney, Dwight R.; White, Steven K.
PATENT ASSIGNEE(S): Hollis-Eden Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 380 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004019953	A1	20040311	WO 2003-US327186		20030828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2496867	AA	20040311	CA 2003-2496867		20030828
AU 2003278744	A1	20040319	AU 2003-278744		20030828
EP 1539183	A1	20050615	EP 2003-770268		20030828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006506445	T2	20060223	JP 2004-569763		20030828
PRIORITY APPLN. INFO.:			US 2002-407146P	P	20020828
			US 2002-408332P	P	20020904
			US 2003-479257P	P	20030617
			WO 2003-US27186	W	20030828

OTHER SOURCE(S): MARPAT 140:229914

AB The invention relates to the use of compds. to ameliorate or treat conditions such as a cystic fibrosis, neutropenia or other exemplified conditions. Exemplary compds. that can be used include 3β-hydroxy-17β-aminoandrost-5-ene, 3β-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3α-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3β-hydroxy-16β-fluoro-17β-aminoandrost-5-ene, 1α,3β-dihydroxy-4α-fluoroandrost-5-ene-17-one, 1α,3β, 17β-trihydroxy-4α-fluorandrost-5-ene, 1β,3β-dihydroxy-6α-bromoandrost-5-ene,

1α-fluoro-3β,12α-dihydroxyandrost-5-ene-17-one,
1α-fluoro-3β,4α-dihydroxyandrost-5-ene and
4α-fluoro-3β,6α, 17β-trihydroxyandrostante.

IT 515159-77-0 515159-78-1 515159-81-6
515159-82-7 515159-83-8 515159-84-9
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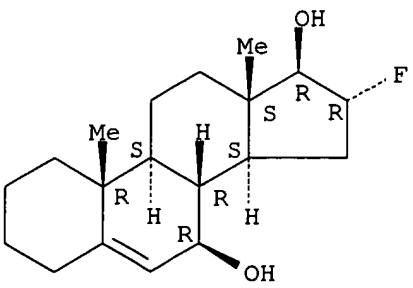
668987-06-2 668987-07-3 668987-08-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory methods and compns. with androgen derivs. and other therapeutic uses)

RN 515159-77-0 CAPLUS
CN Androst-5-ene-7,17-diol, 16-fluoro-, (7β,16α,17β)- (9CI) (CA INDEX NAME)

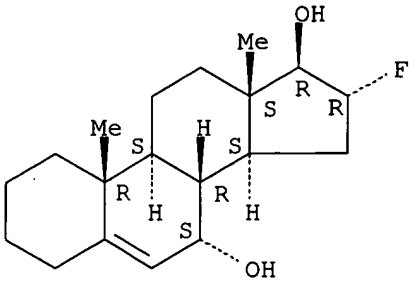
Absolute stereochemistry.



RN 515159-78-1 CAPLUS
CN Androst-5-ene-7,17-diol, 16-fluoro-, (7α,16α,17β)- (9CI)

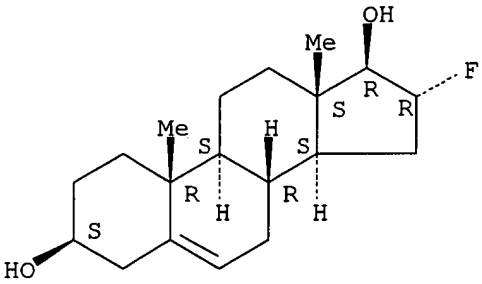
(CA INDEX NAME)

Absolute stereochemistry.



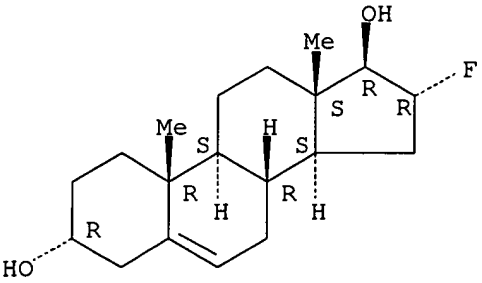
RN 515159-81-6 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



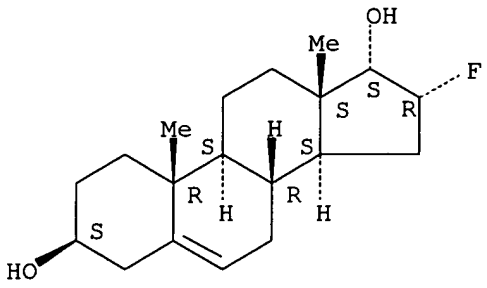
RN 515159-82-7 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3α,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



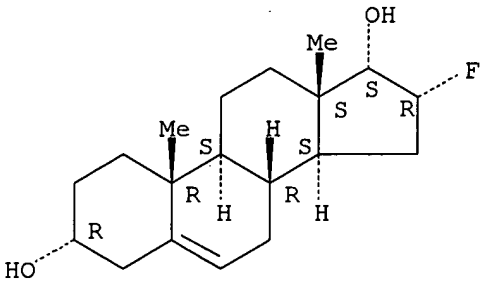
RN 515159-83-8 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3β,16α,17α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



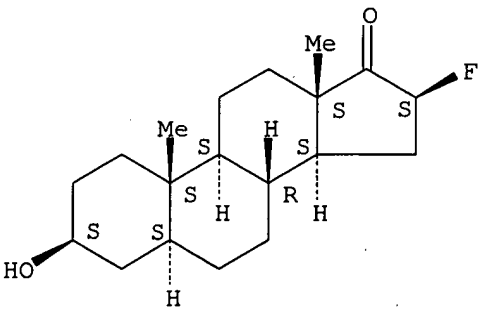
RN 515159-84-9 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3α,16α,17α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



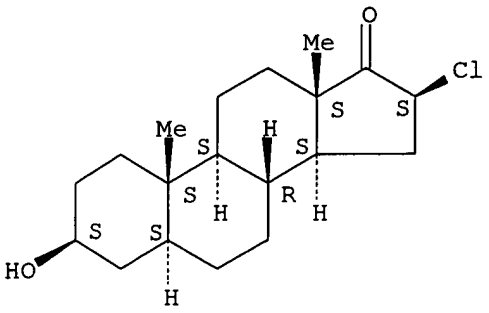
RN 668986-06-9 CAPLUS
CN Androstan-17-one, 16-fluoro-3-hydroxy-, (3β,5α,16β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



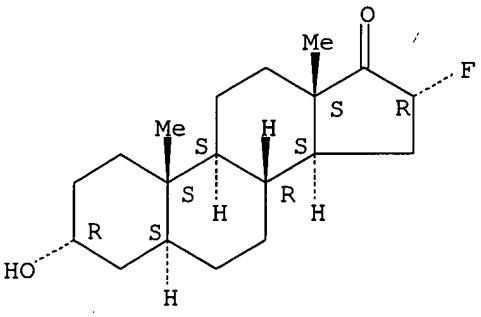
RN 668986-07-0 CAPLUS
CN Androstan-17-one, 16-chloro-3-hydroxy-, (3β,5α,16β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



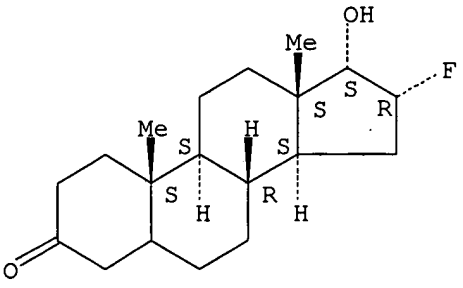
RN 668986-08-1 CAPLUS
CN Androstan-17-one, 16-fluoro-3-hydroxy-, (3α,5α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



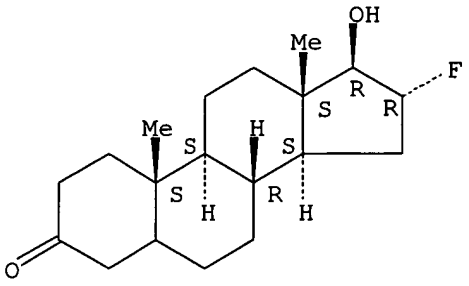
RN 668986-09-2 CAPLUS
CN Androstan-3-one, 16-fluoro-17-hydroxy-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



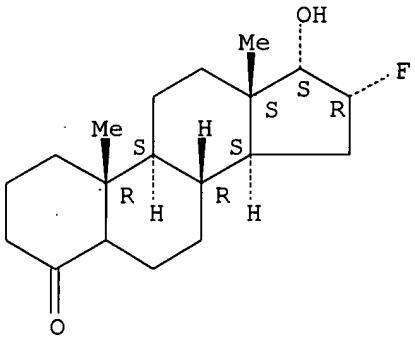
RN 668986-10-5 CAPLUS
CN Androstan-3-one, 16-fluoro-17-hydroxy-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



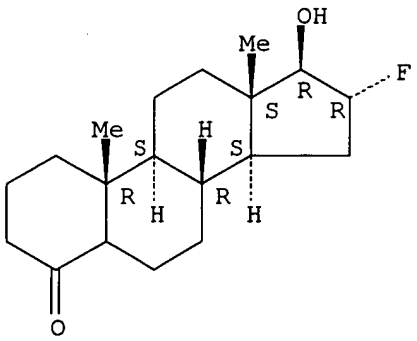
RN 668986-11-6 CAPLUS
CN Androstan-4-one, 16-fluoro-17-hydroxy-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



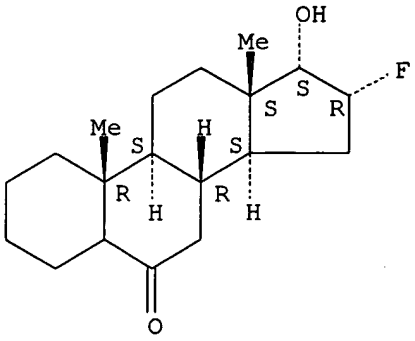
RN 668986-12-7 CAPLUS
CN Androstan-4-one, 16-fluoro-17-hydroxy-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



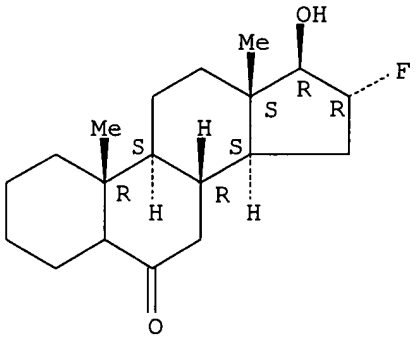
RN 668986-13-8 CAPLUS
CN Androstan-6-one, 16-fluoro-17-hydroxy-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



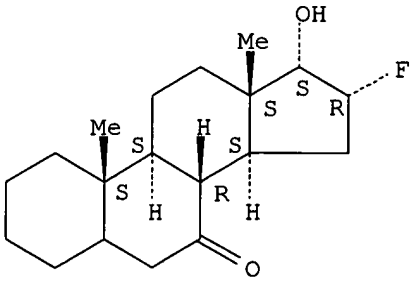
RN 668986-14-9 CAPLUS
CN Androstan-6-one, 16-fluoro-17-hydroxy-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



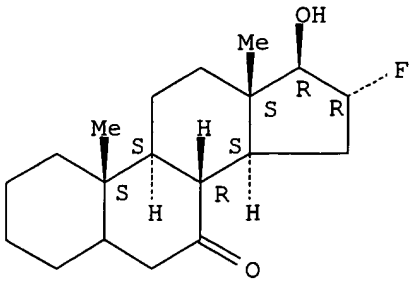
RN 668986-15-0 CAPLUS
CN Androstan-7-one, 16-fluoro-17-hydroxy-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



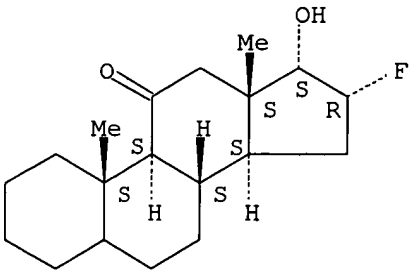
RN 668986-16-1 CAPLUS
CN Androstan-7-one, 16-fluoro-17-hydroxy-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



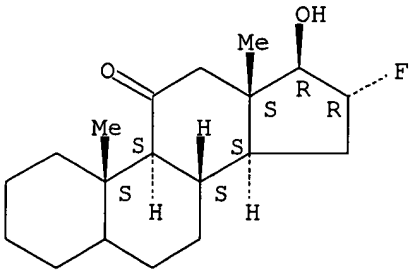
RN 668986-17-2 CAPLUS
CN Androstan-11-one, 16-fluoro-17-hydroxy-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



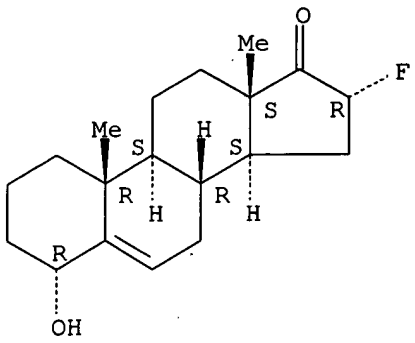
RN 668986-18-3 CAPLUS
CN Androstan-11-one, 16-fluoro-17-hydroxy-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



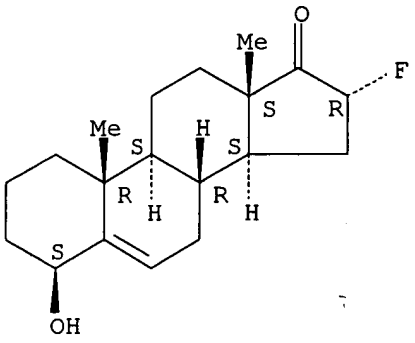
RN 668986-19-4 CAPLUS
CN Androst-5-en-17-one, 16-fluoro-4-hydroxy-, (4α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



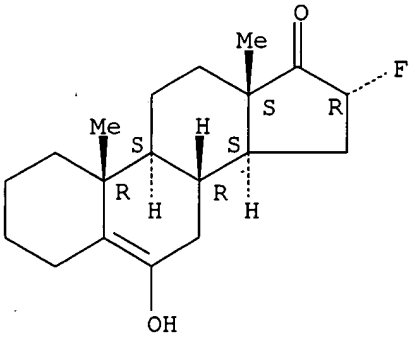
RN 668986-20-7 CAPLUS
CN Androst-5-en-17-one, 16-fluoro-4-hydroxy-, (4β,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



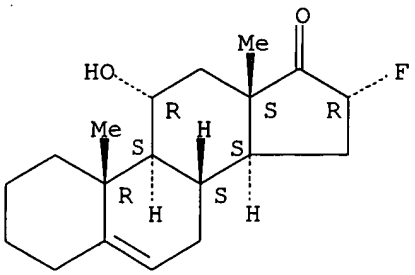
RN 668986-21-8 CAPLUS
CN Androst-5-en-17-one, 16-fluoro-6-hydroxy-, (16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



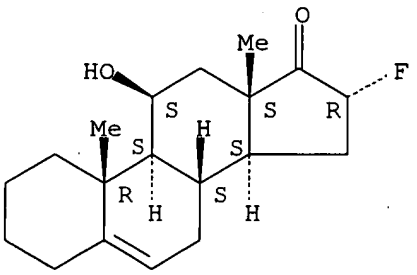
RN 668986-22-9 CAPLUS
CN Androst-5-en-17-one, 16-fluoro-11-hydroxy-, (11α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



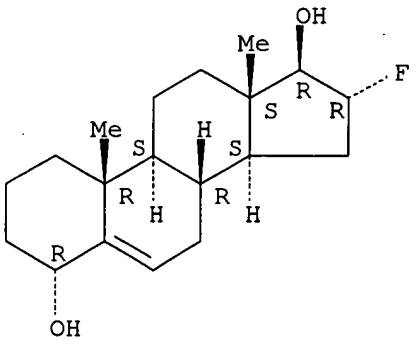
RN 668986-23-0 CAPLUS
CN Androst-5-en-17-one, 16-fluoro-11-hydroxy-, (11β,16α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



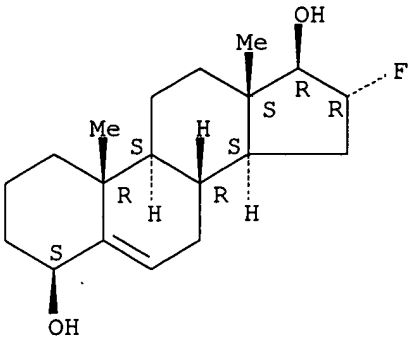
RN 668986-24-1 CAPLUS
CN Androst-5-ene-4,17-diol, 16-fluoro-, (4α,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



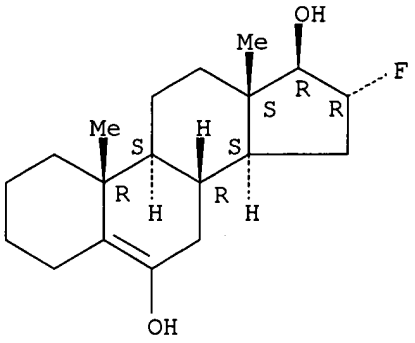
RN 668986-25-2 CAPLUS
CN Androst-5-ene-4,17-diol, 16-fluoro-, (4β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



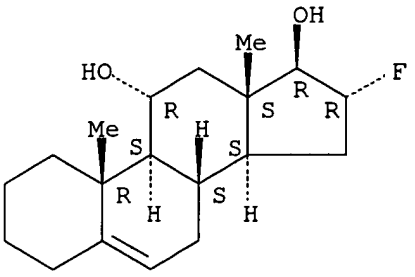
RN 668986-26-3 CAPLUS
CN Androst-5-ene-6,17-diol, 16-fluoro-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



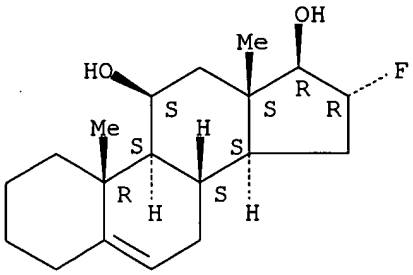
RN 668986-27-4 CAPLUS
CN Androst-5-ene-11,17-diol, 16-fluoro-, (11α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



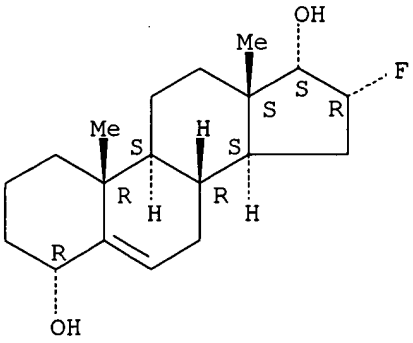
RN 668986-28-5 CAPLUS
CN Androst-5-ene-11,17-diol, 16-fluoro-, (11β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



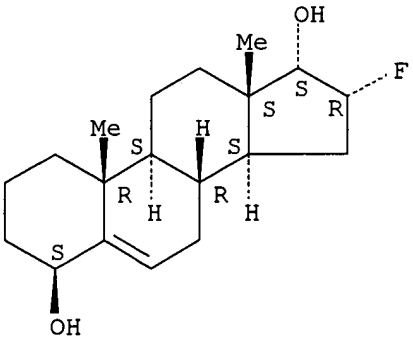
RN 668986-29-6 CAPLUS
CN Androst-5-ene-4,17-diol, 16-fluoro-, (4α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



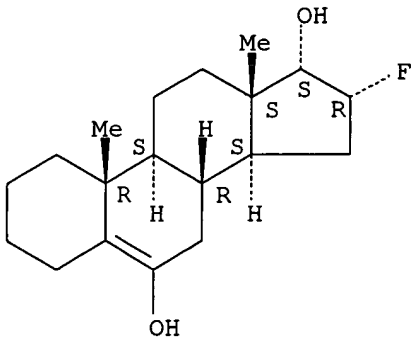
RN 668986-30-9 CAPLUS
CN Androst-5-ene-4,17-diol, 16-fluoro-, (4β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



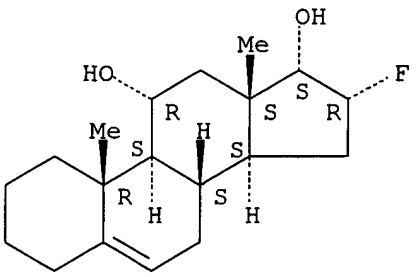
RN 668986-31-0 CAPLUS
CN Androst-5-ene-6,17-diol, 16-fluoro-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



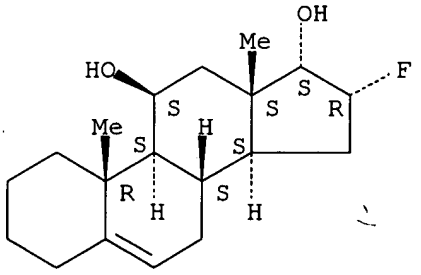
RN 668986-32-1 CAPLUS
CN Androst-5-ene-11,17-diol, 16-fluoro-, (11α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



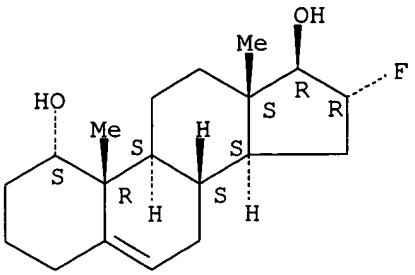
RN 668986-33-2 CAPLUS
CN Androst-5-ene-11,17-diol, 16-fluoro-, (11β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



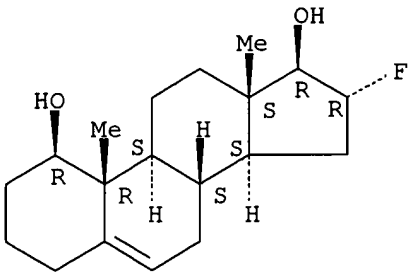
RN 668986-34-3 CAPLUS
CN Androst-5-ene-1,17-diol, 16-fluoro-, (1α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



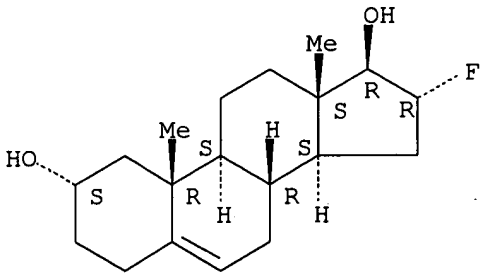
RN 668986-35-4 CAPLUS
CN Androst-5-ene-1,17-diol, 16-fluoro-, (1β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



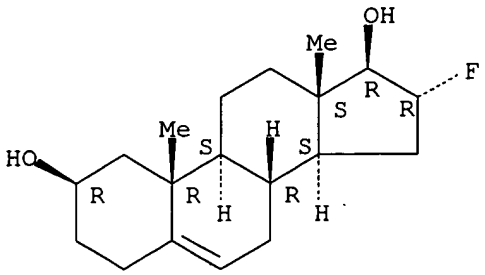
RN 668986-36-5 CAPLUS
CN Androst-5-ene-2,17-diol, 16-fluoro-, (2α,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



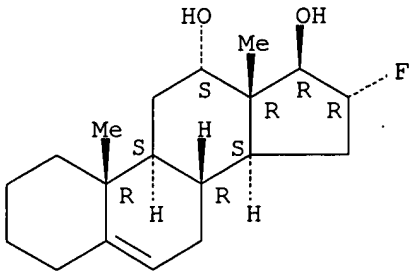
RN 668986-37-6 CAPLUS
CN Androst-5-ene-2,17-diol, 16-fluoro-, (2β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



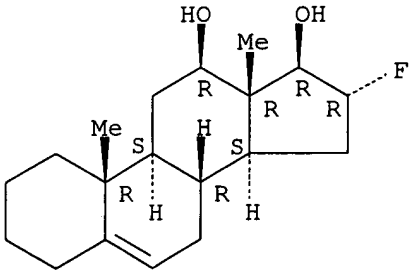
RN 668986-38-7 CAPLUS
CN Androst-5-ene-12,17-diol, 16-fluoro-, (12α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



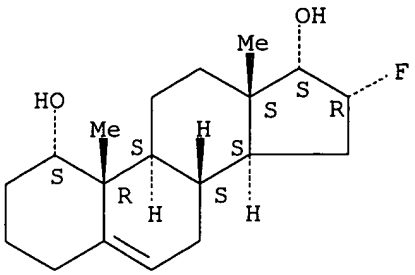
RN 668986-39-8 CAPLUS
CN Androst-5-ene-12,17-diol, 16-fluoro-, (12β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



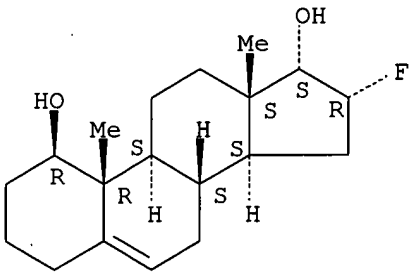
RN 668986-40-1 CAPLUS
CN Androst-5-ene-1,17-diol, 16-fluoro-, (1α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



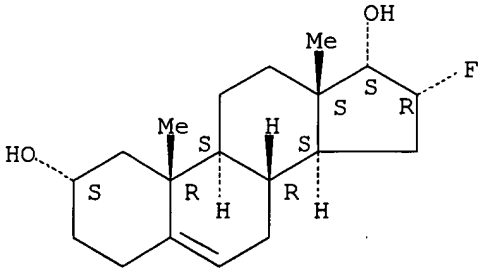
RN 668986-41-2 CAPLUS
CN Androst-5-ene-1,17-diol, 16-fluoro-, (1β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



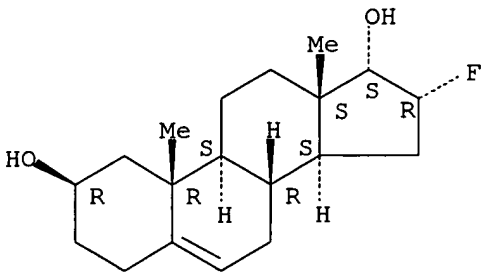
RN 668986-42-3 CAPLUS
CN Androst-5-ene-2,17-diol, 16-fluoro-, (2α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



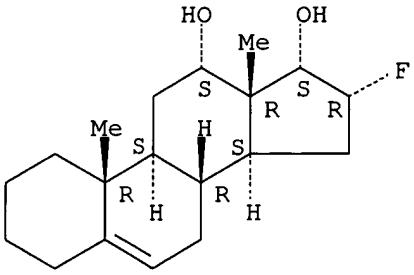
RN 668986-43-4 CAPLUS
CN Androst-5-ene-2,17-diol, 16-fluoro-, (2β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



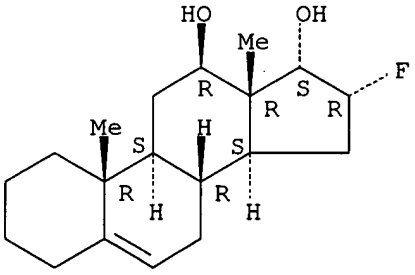
RN 668986-44-5 CAPLUS
CN Androst-5-ene-12,17-diol, 16-fluoro-, (12α,16α,17α)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



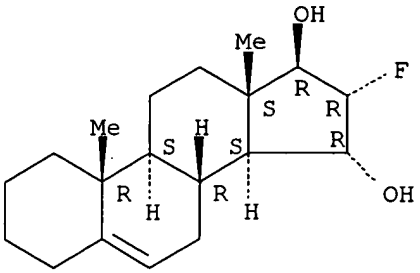
RN 668986-45-6 CAPLUS
CN Androst-5-ene-12,17-diol, 16-fluoro-, (12β,16α,17α)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



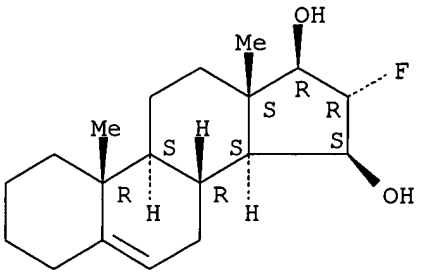
RN 668986-46-7 CAPLUS
CN Androst-5-ene-15,17-diol, 16-fluoro-, (15α,16α,17β)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



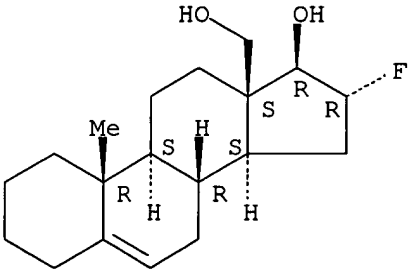
RN 668986-47-8 CAPLUS
CN Androst-5-ene-15,17-diol, 16-fluoro-, (15β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



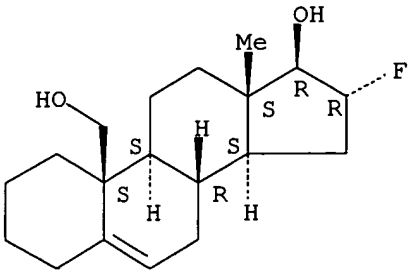
RN 668986-48-9 CAPLUS
CN Androst-5-ene-17,18-diol, 16-fluoro-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



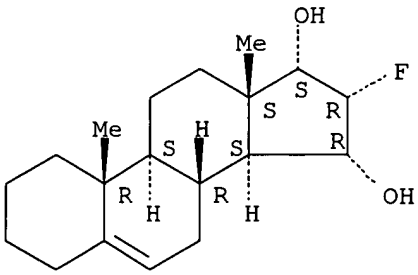
RN 668986-49-0 CAPLUS
CN Androst-5-ene-17,19-diol, 16-fluoro-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



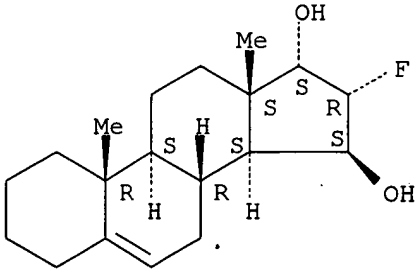
RN 668986-50-3 CAPLUS
CN Androst-5-ene-15,17-diol, 16-fluoro-, (15α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



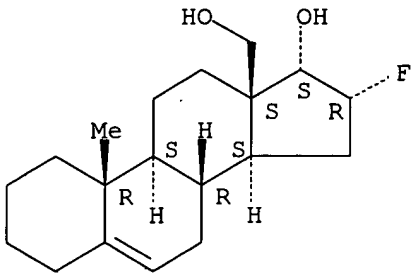
RN 668986-51-4 CAPLUS
CN Androst-5-ene-15,17-diol, 16-fluoro-, (15β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



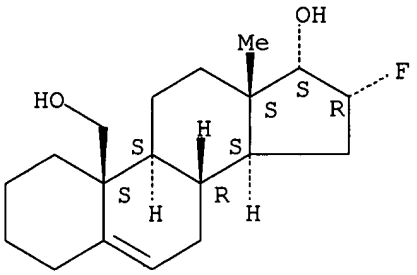
RN 668986-52-5 CAPLUS
CN Androst-5-ene-17,18-diol, 16-fluoro-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



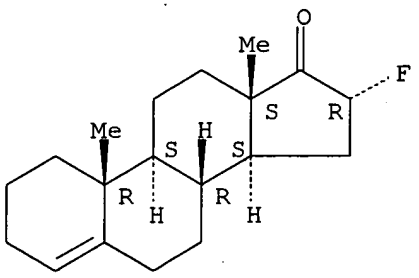
RN 668986-53-6 CAPLUS
CN Androst-5-ene-17,19-diol, 16-fluoro-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



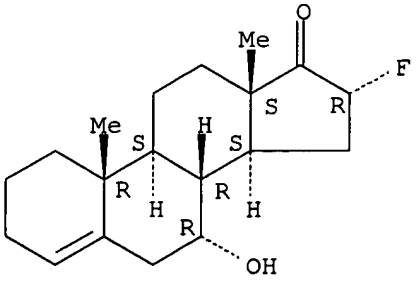
RN 668986-54-7 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-, (16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



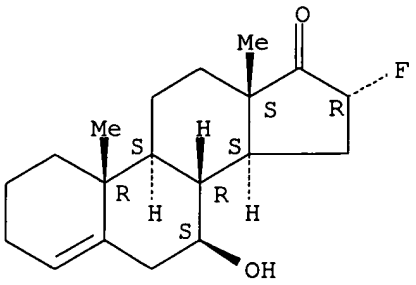
RN 668986-55-8 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-7-hydroxy-, (7α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



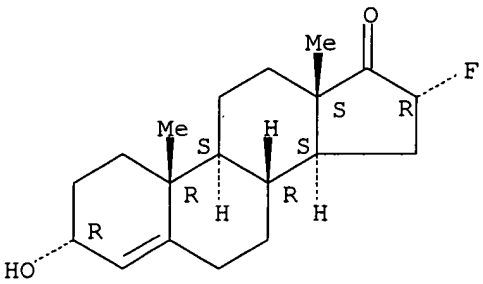
RN 668986-56-9 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-7-hydroxy-, (7β,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



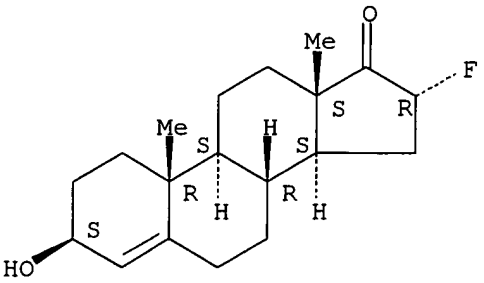
RN 668986-57-0 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-3-hydroxy-, (3α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



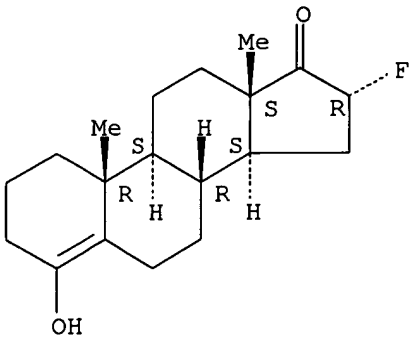
RN 668986-58-1 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-3-hydroxy-, (3β,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



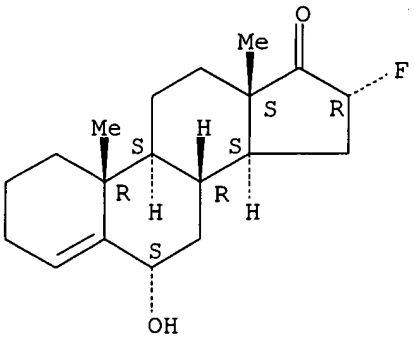
RN 668986-59-2 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-4-hydroxy-, (16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



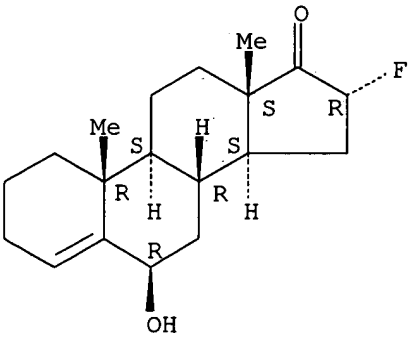
RN 668986-60-5 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-6-hydroxy-, (6α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



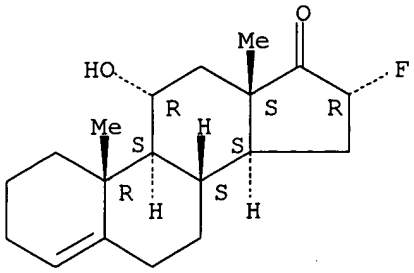
RN 668986-61-6 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-6-hydroxy-, (6β,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



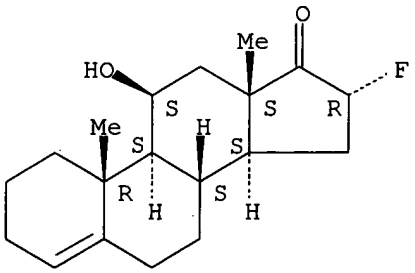
RN 668986-63-8 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-11-hydroxy-, (11α,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



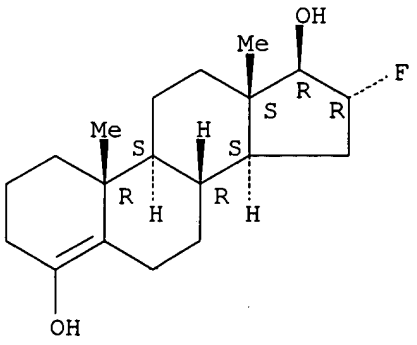
RN 668986-64-9 CAPLUS
CN Androst-4-en-17-one, 16-fluoro-11-hydroxy-, (11β,16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



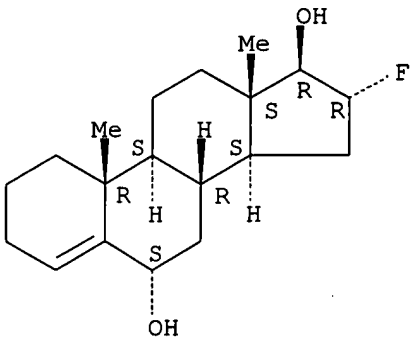
RN 668986-65-0 CAPLUS
CN Androst-4-ene-4,17-diol, 16-fluoro-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



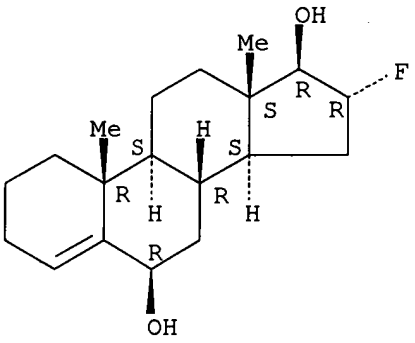
RN 668986-66-1 CAPLUS
CN Androst-4-ene-6,17-diol, 16-fluoro-, (6α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



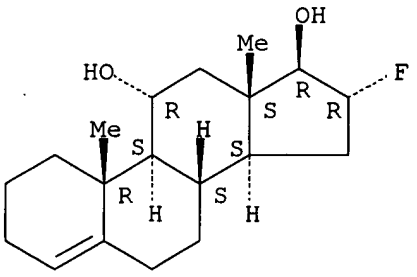
RN 668986-67-2 CAPLUS
CN Androst-4-ene-6,17-diol, 16-fluoro-, (6β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



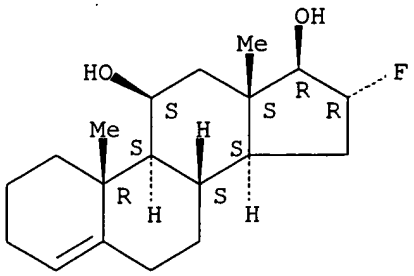
RN 668986-68-3 CAPLUS
CN Androst-4-ene-11,17-diol, 16-fluoro-, (11α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



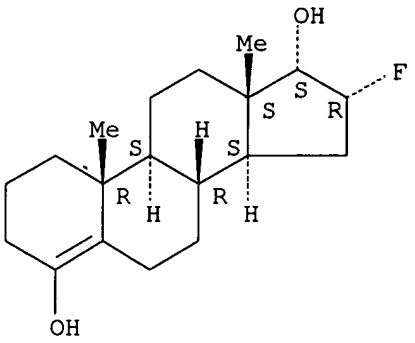
RN 668986-69-4 CAPLUS
CN Androst-4-ene-11,17-diol, 16-fluoro-, (11β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



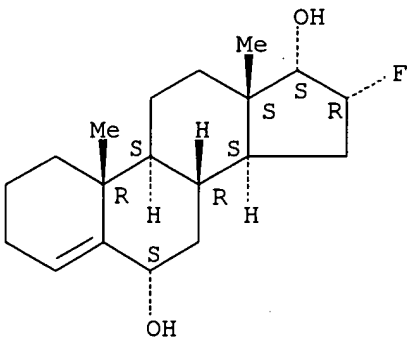
RN 668986-70-7 CAPLUS
CN Androst-4-ene-4,17-diol, 16-fluoro-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



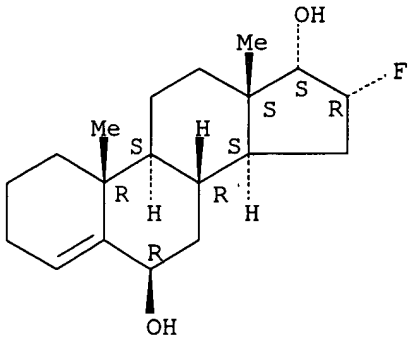
RN 668986-71-8 CAPLUS
CN Androst-4-ene-6,17-diol, 16-fluoro-, (6α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



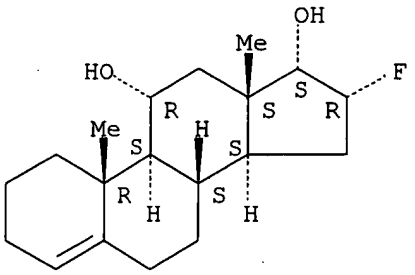
RN 668986-72-9 CAPLUS
CN Androst-4-ene-6,17-diol, 16-fluoro-, (6β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



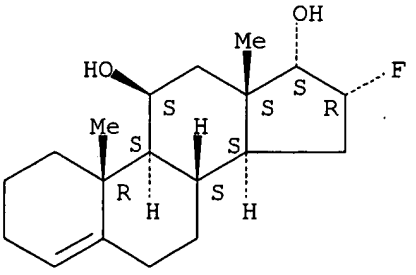
RN 668986-73-0 CAPLUS
CN Androst-4-ene-11,17-diol, 16-fluoro-, (11α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



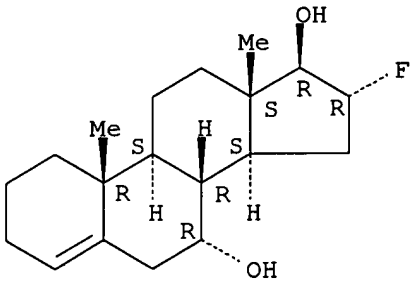
RN 668986-74-1 CAPLUS
CN Androst-4-ene-11,17-diol, 16-fluoro-, (11β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



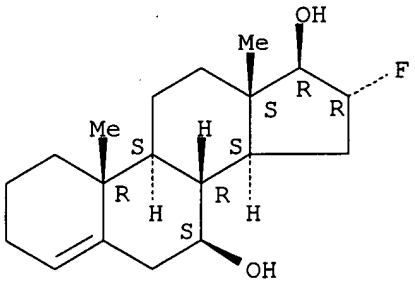
RN 668986-75-2 CAPLUS
CN Androst-4-ene-7,17-diol, 16-fluoro-, (7α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



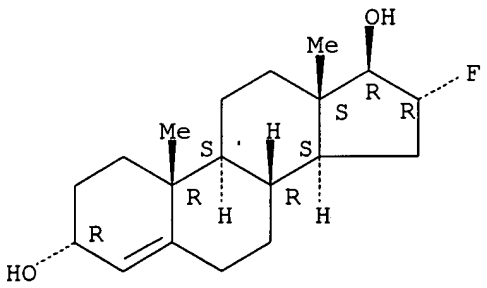
RN 668986-76-3 CAPLUS
CN Androst-4-ene-7,17-diol, 16-fluoro-, (7β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



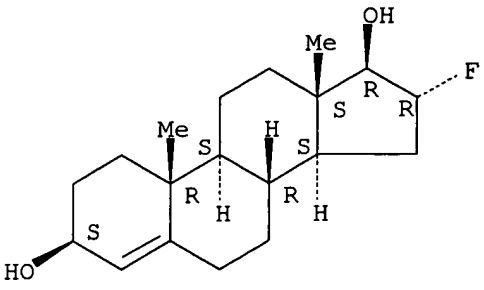
RN 668986-77-4 CAPLUS
CN Androst-4-ene-3,17-diol, 16-fluoro-, (3α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



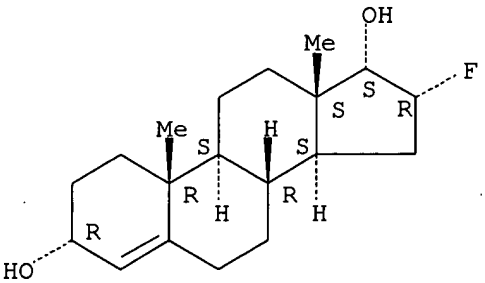
RN 668986-78-5 CAPLUS
CN Androst-4-ene-3,17-diol, 16-fluoro-, (3β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



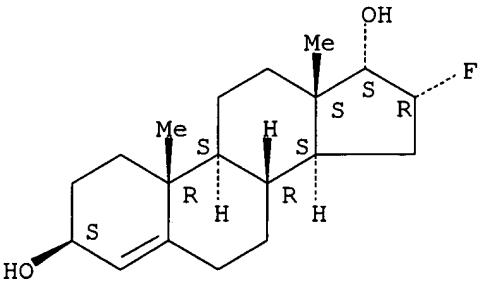
RN 668986-79-6 CAPLUS
CN Androst-4-ene-3,17-diol, 16-fluoro-, (3α,16α,17α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



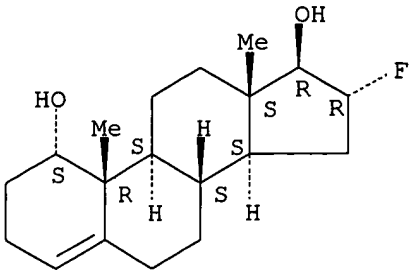
RN 668986-80-9 CAPLUS
CN Androst-4-ene-3,17-diol, 16-fluoro-, (3β,16α,17α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



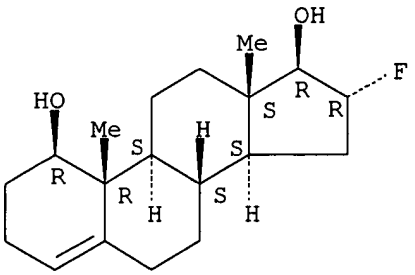
RN 668986-81-0 CAPLUS
CN Androst-4-ene-1,17-diol, 16-fluoro-, (1α,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



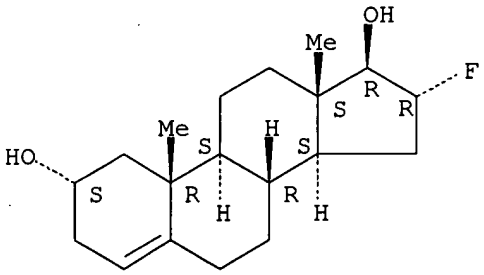
RN 668986-82-1 CAPLUS
CN Androst-4-ene-1,17-diol, 16-fluoro-, (1β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



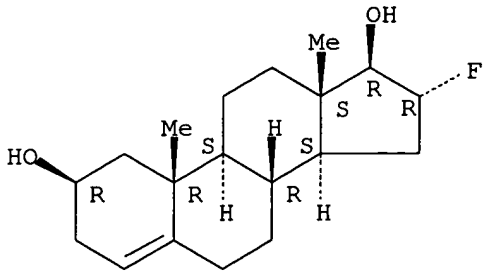
RN 668986-83-2 CAPLUS
CN Androst-4-ene-2,17-diol, 16-fluoro-, (2α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



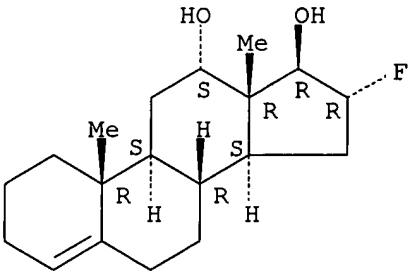
RN 668986-84-3 CAPLUS
CN Androst-4-ene-2,17-diol, 16-fluoro-, (2β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



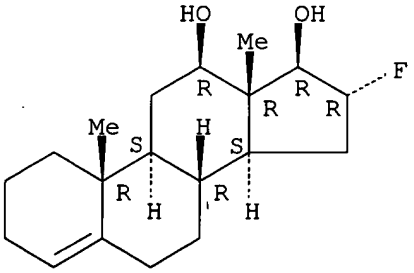
RN 668986-85-4 CAPLUS
CN Androst-4-ene-12,17-diol, 16-fluoro-, (12α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



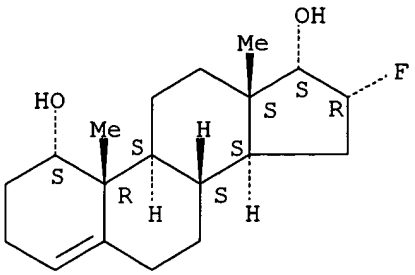
RN 668986-86-5 CAPLUS
CN Androst-4-ene-12,17-diol, 16-fluoro-, (12β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



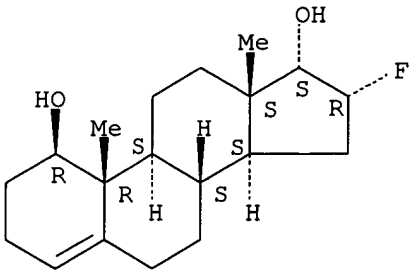
RN 668986-87-6 CAPLUS
CN Androst-4-ene-1,17-diol, 16-fluoro-, (1α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



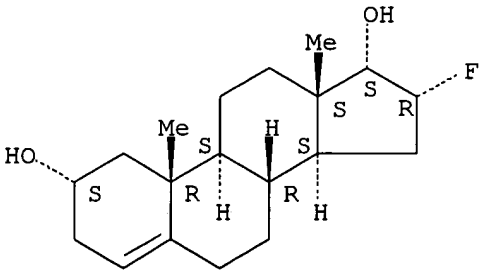
RN 668986-88-7 CAPLUS
CN Androst-4-ene-1,17-diol, 16-fluoro-, (1β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



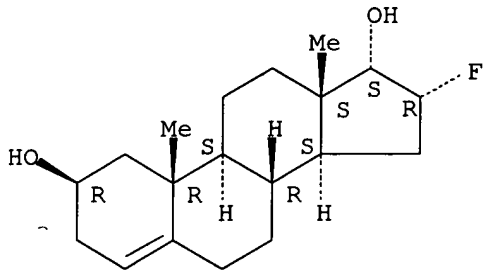
RN 668986-89-8 CAPLUS
CN Androst-4-ene-2,17-diol, 16-fluoro-, (2α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



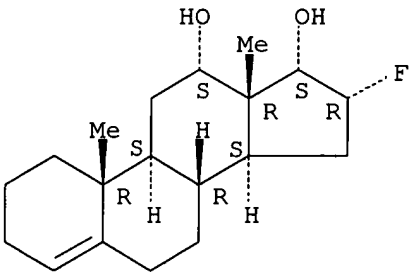
RN 668986-90-1 CAPLUS
CN Androst-4-ene-2,17-diol, 16-fluoro-, (2β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



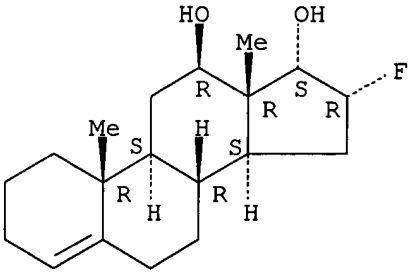
RN 668986-91-2 CAPLUS
CN Androst-4-ene-12,17-diol, 16-fluoro-, (12α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



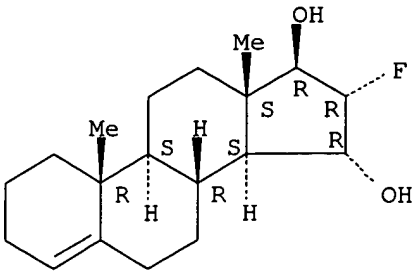
RN 668986-92-3 CAPLUS
CN Androst-4-ene-12,17-diol, 16-fluoro-, (12β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



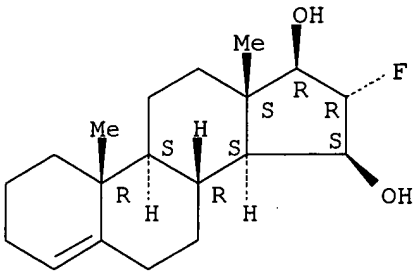
RN 668986-93-4 CAPLUS
CN Androst-4-ene-15,17-diol, 16-fluoro-, (15α,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



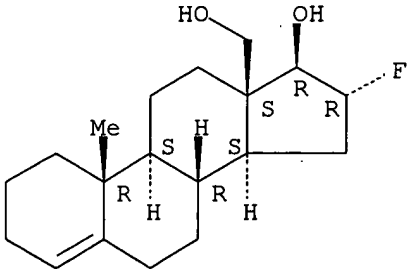
RN 668986-94-5 CAPLUS
CN Androst-4-ene-15,17-diol, 16-fluoro-, (15β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



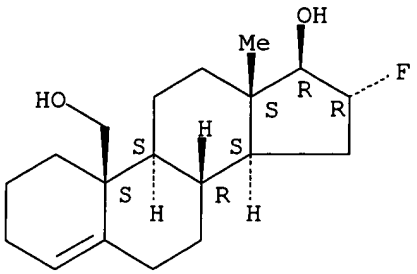
RN 668986-95-6 CAPLUS
CN Androst-4-ene-17,18-diol, 16-fluoro-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



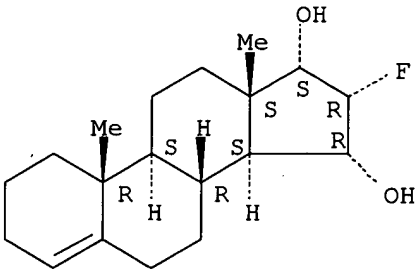
RN 668986-96-7 CAPLUS
CN Androst-4-ene-17,19-diol, 16-fluoro-, (16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



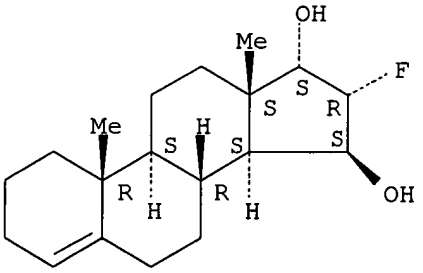
RN 668986-97-8 CAPLUS
CN Androst-4-ene-15,17-diol, 16-fluoro-, (15α,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



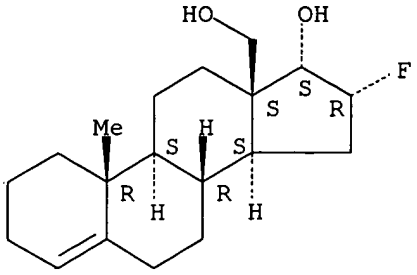
RN 668986-98-9 CAPLUS
CN Androst-4-ene-15,17-diol, 16-fluoro-, (15β,16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



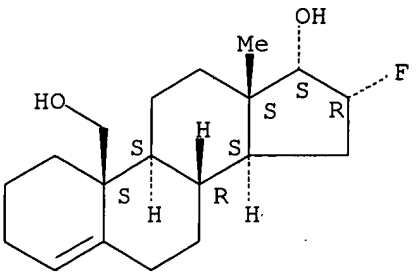
RN 668986-99-0 CAPLUS
CN Androst-4-ene-17,18-diol, 16-fluoro-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



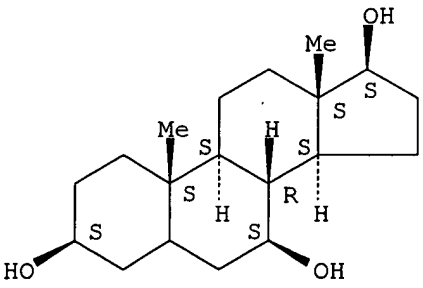
RN 668987-00-6 CAPLUS
CN Androst-4-ene-17,19-diol, 16-fluoro-, (16α,17α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



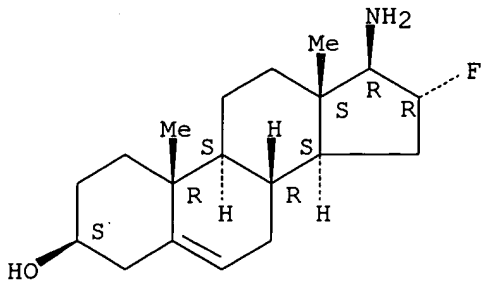
RN 668987-01-7 CAPLUS
CN Androstane-3,7,17-triol, (3β,7β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



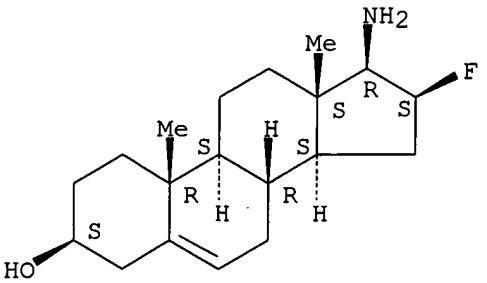
RN 668987-02-8 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16-fluoro-, (3β,16α,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



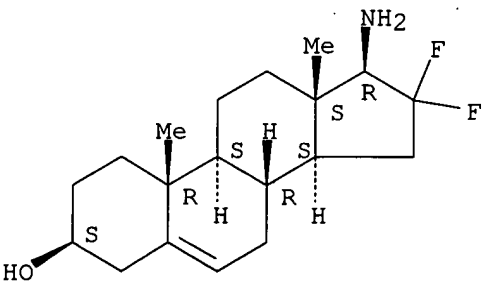
RN 668987-03-9 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16-fluoro-, (3β,16β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



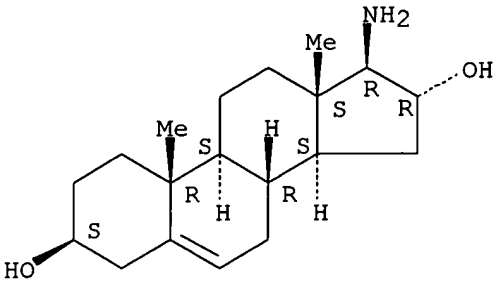
RN 668987-04-0 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-difluoro-, (3β,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



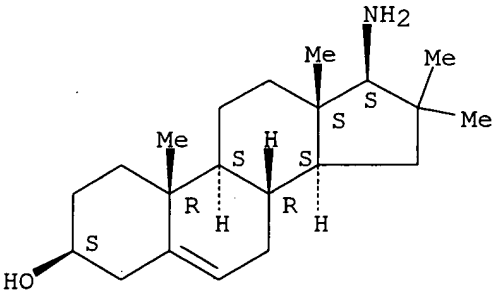
RN 668987-05-1 CAPLUS
CN Androst-5-ene-3,16-diol, 17-amino-, (3β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



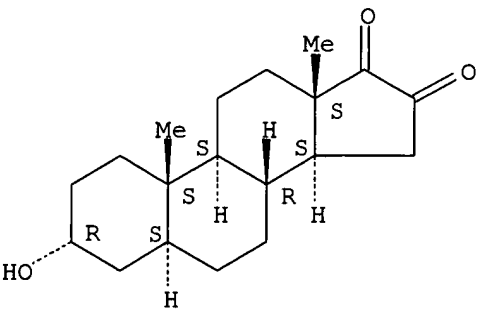
RN 668987-06-2 CAPLUS
CN Androst-5-en-3-ol, 17-amino-16,16-dimethyl-, (3β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



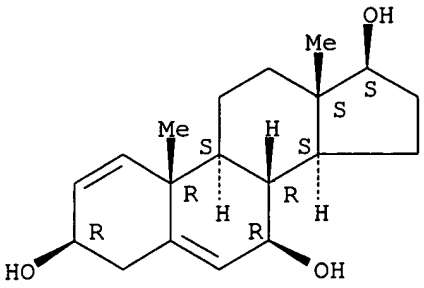
RN 668987-07-3 CAPLUS
CN Androstane-16,17-dione, 3-hydroxy-, (3α,5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 668987-08-4 CAPLUS
CN Androsta-1,5-diene-3,7,17-triol, (3β,7β,17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:334636 CAPLUS
DOCUMENT NUMBER: 138:332206
TITLE: Methods and synthesis of compounds for the treatment of blood cell disorders and delayed adverse and unwanted effect of radiation exposure
INVENTOR(S): Ahlem, Clarence N.; Reading, Christopher; Frincke, James; Stickney, Dwight; Lardy, Henry A.; Marwah, Padma; Marwah, Ashok; Prendergast, Patrick T.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 198 pp., Cont.-in-part of U.S. Ser. No. 675,470.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003083231	A1	20030501	US 2002-87929	20020301
US 6667299	B1	20031223	US 2000-535675	20000323
EP 1422234	A2	20040526	EP 2004-3521	20000323
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 2003060425	A1	20030327	US 2001-820483	20010329
ZA 2001003845	A	20020513	ZA 2001-3845	20010511
ZA 2001003852	A	20020611	ZA 2001-3852	20010511
ZA 2001006980	A	20030123	ZA 2001-6980	20010823
ZA 2003006638	A	20040826	ZA 2003-6638	20020301
US 2004043973	A1	20040304	US 2002-319356	20021213
US 2004116359	A1	20040617	US 2002-329065	20021221
US 2004220114	A1	20041104	US 2003-602330	20030623
US 2004097406	A1	20040520	US 2003-607035	20030625
US 2006063749	A1	20060323	US 2003-607415	20030625
US 2004220161	A1	20041104	US 2003-741929	20031219
US 2005282732	A1	20051222	US 2004-876957	20040624
US 2005159366	A1	20050721	US 2004-890490	20040713
US 2005075321	A1	20050407	US 2004-949782	20040923
US 2005256095	A1	20051117	US 2004-949694	20040923
US 2006079492	A1	20060413	US 2005-234675	20050923

PRIORITY APPLN. INFO.:

US 1998-109923P	P	19981124
US 1998-109924P	P	19981124
US 1998-110127P	P	19981127
US 1998-112206P	P	19981215
US 1999-124087P	P	19990311
US 1999-126056P	P	19990323
US 1999-137745P	P	19990603

US 1999-140028P	P	19990616
US 1999-145823P	P	19990727
US 1999-414905	B2	19991008
US 1999-161453P	P	19991025
US 1999-449004	B2	19991124
US 1999-449042	B2	19991124
US 1999-449184	B2	19991124
US 1999-461026	B2	19991215
US 2000-535675	A2	20000323
US 2000-586672	B2	20000601
US 2000-586673	B2	20000601
US 2000-675470	A2	20000928
US 2001-272624P	P	20010301
US 2001-820483	A2	20010329
US 2001-323016P	P	20010910
US 2001-328738P	P	20011011
US 2001-338015P	P	20011108
US 2001-340045P	P	20011130
US 2001-343523P	P	20011220
US 1999-164048P	P	19991108
US 2000-190140P	P	20000316
EP 2000-918365	A3	20000323
US 2000-257071P	P	20001220
US 2002-87929	A3	20020301
US 2002-329065	A1	20021221

OTHER SOURCE(S): MARPAT 138:332206

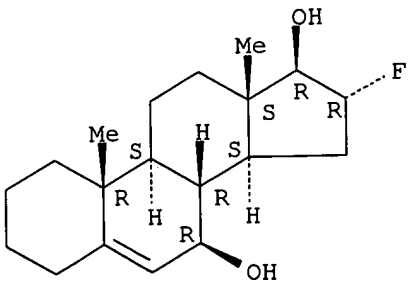
AB The invention relates to the use of compds. to treat a number of conditions, such as blood cell disorders and symptoms and conditions associated with delayed adverse or unwanted effects of radiation therapy. Compds. that can be used in the invention include methyl-2,3,4-trihydroxy-1-O-(7,17-dioxoandrost-5-ene-3β-yl)-β-D-glucopyranosiduronate, 16α,3α-dihydroxy-5α-androstan-17-one or 3,7,16,17-tetrahydroxyandrost-5-ene, 3,7,16,17-tetrahydroxyandrost-4-ene,3,7,16,17-tetrahydroxyandrost-1-ene or 3,7,16,17-tetrahydroxyandrostane that can be used in the treatment method. Methods for the synthesis of those compds. are exemplified. Formulation and dosage of those compds. are claimed.

IT 515159-77-0P 515159-78-1P 515159-81-6P
515159-82-7P 515159-83-8P 515159-84-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods and synthesis of compds. for treatment of blood cell disorders and delayed adverse and unwanted effect of radiation exposure)

RN 515159-77-0 CAPLUS

CN Androst-5-ene-7,17-diol, 16-fluoro-, (7β,16α,17β)- (9CI) (CA INDEX NAME)

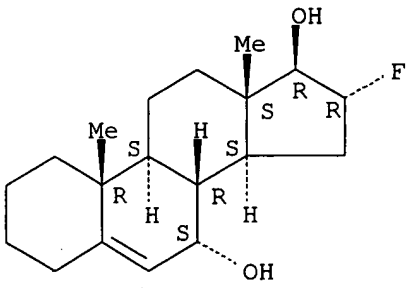
Absolute stereochemistry.



RN 515159-78-1 CAPLUS

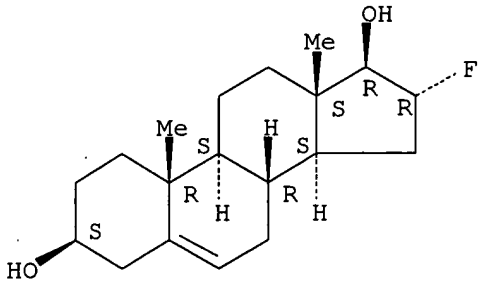
CN Androst-5-ene-7,17-diol, 16-fluoro-, (7α,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



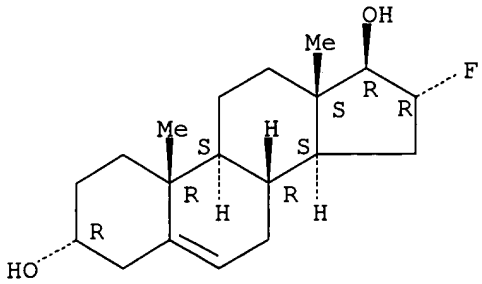
RN 515159-81-6 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3β,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



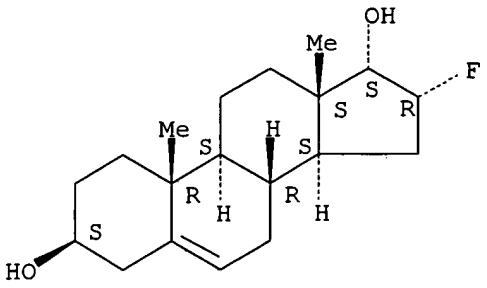
RN 515159-82-7 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3α,16α,17β)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



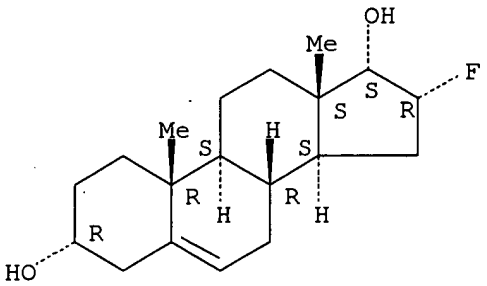
RN 515159-83-8 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3β,16α,17α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RN 515159-84-9 CAPLUS
CN Androst-5-ene-3,17-diol, 16-fluoro-, (3α,16α,17α)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



```
=> s l13 and (graft or graft versus host or organ rejection or organ tranplant?)
         99013 GRAFT
         14304 GRAFTS
        104892 GRAFT
                (GRAFT OR GRAFTS)
         99013 GRAFT
         14304 GRAFTS
        104892 GRAFT
                (GRAFT OR GRAFTS)
         31328 VERSUS
        202097 HOST
         23619 HOSTS
        215043 HOST
                (HOST OR HOSTS)
          1700 GRAFT VERSUS HOST
                (GRAFT(W)VERSUS(W)HOST)
        124703 ORGAN
        117747 ORGANS
        208438 ORGAN
                (ORGAN OR ORGANS)
         34140 REJECTION
          1422 REJECTIONS
         34740 REJECTION
                (REJECTION OR REJECTIONS)
           252 ORGAN REJECTION
                (ORGAN(W)REJECTION)
        124703 ORGAN
        117747 ORGANS
        208438 ORGAN
                (ORGAN OR ORGANS)
            44 TRANPLANT?
             1 ORGAN TRANPLANT?
                (ORGAN(W)TRANPLANT?)
L14        2344 L13 AND (GRAFT OR GRAFT VERSUS HOST OR ORGAN REJECTION OR ORGAN
                TRANPLANT?)

=> s l4 and (androst? or androstene)
         32608 ANDROST?
          4665 ANDROSTENE
           406 ANDROSTENES
          4888 ANDROSTENE
                (ANDROSTENE OR ANDROSTENES)
L15           0 L4 AND (ANDROST? OR ANDROSTENE)

=> s l14 and (androst? or androstene)
         32608 ANDROST?
          4665 ANDROSTENE
           406 ANDROSTENES
          4888 ANDROSTENE
                (ANDROSTENE OR ANDROSTENES)
L16          19 L14 AND (ANDROST? OR ANDROSTENE)

=> d ibib abs 1-16

L16  ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:491792  CAPLUS
DOCUMENT NUMBER:          145:14124
TITLE:                    Topical delivery system comprising esters of hydroxy
                          acids for cosmetic and pharmaceutical agents
INVENTOR(S):              Gupta, Shyam K.
PATENT ASSIGNEE(S):       Bioderm Research, USA
SOURCE:                   U.S. Pat. Appl. Publ., 20 pp.
```

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006110415	A1	20060525	US 2004-904665	20041122

PRIORITY APPLN. INFO.: US 2004-904665 20041122

AB This invention relates to topical compns. containing esters of hydroxy acids and their application in the deep-penetration delivery of beneficial cosmetic and pharmaceutical agents. An ester of a hydroxy acid is selected from alkyl and aryl esters of glycolic, malic, lactic, mandelic, ascorbic, phytic, salicylic, aleuritic, tartaric, etc. acids. Thus, a skin whitening serum was prepared containing Et Lactate 20.0, hydroxypropyl guar 0.5,, quinacetophenone 5.0, PEG-6 70.0, arbutin 4.0, and preservatives 0.5 parts, resp. The product had a clear to slight hazy serum-like appearance. It was absorbed rapidly with a silky smooth skin feel. Also, an arthritis pain relief anti-inflammatory gel was prepared containing tri-Et citrate 55.65, Polyamide-3 5.0, preservative 0.5, Boswellia serrata extract 0.05, N-acetyl-glucosamine 2.0, methylsulfonylmethane 5.0, Aloe vera 0.1, vitamin E 0.5, paeonol 0.5, magnolol 0.2, chondroitin sulfate 0.5, and zeolite 30.0 parts, resp.

L16 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:411062 CAPLUS
DOCUMENT NUMBER: 142:442337
TITLE: Therapeutic use of androgens for various conditions including cardiovascular disease, immune disorders, trauma, and inflammation
INVENTOR(S): Reading, Christopher L.; Ahlem, Clarence N.; Auci, Dominick L.; Dowding, Charles; Frincke, James M.; Li, Mei; Page, Theodore M.; Stickney, Dwight R.; Trauger, Richard J.; White, Steven K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 180 pp., Cont.-in-part of U.S. Ser. No. 651,515.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005101581	A1	20050512	US 2003-728400		20031205
US 2004138187	A1	20040715	US 2003-651515		20030828
PRIORITY APPLN. INFO.:			US 2002-407146P	P	20020828
			US 2002-408332P	P	20020904
			US 2003-479257P	P	20030617
			US 2003-651515	A2	20030828

OTHER SOURCE(S): MARPAT 142:442337

AB The invention relates to the use of compds. to ameliorate or treat a condition such as a cystic fibrosis, neutropenia or other exemplified conditions including cardiovascular disease, immune disorders, trauma, and inflammation. Exemplary compds. that can be used include 3β-hydroxy-17β-aminoandrost-5-ene, 3β-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3α-hydroxy-16α-fluoro-17β-aminoandrost-5-ene, 3β-hydroxy-16β-fluoro-17β-aminoandrost-5-ene, 1α,3β-dihydroxy-4α-fluoroandrost-5-ene-17-one, 1α,3β, 17β-trihydroxy-4α-fluorandrost-5-

ene, 1β,3β-dihydroxy-6α-bromoandrost-5-ene, 1α-fluoro-3β,12α-dihydroxyandrost-5-ene-17-one, 1α-fluoro-3β,4α-dihydroxyandrost-5-ene and 4α-fluoro-3β,6α, 17β-trihydroxyandrostane.

L16 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:53338 CAPLUS
DOCUMENT NUMBER: 142:232308
TITLE: Liver grafts preserved in celsior solution as source of hepatocytes for drug metabolism studies: Comparison with surgical liver biopsies
AUTHOR(S): Donato, M. Teresa; Serralta, Alfonso; Jimenez, Nuria; Perez, Gabriela; Castell, Jose V.; Mir, Jose; Gomez-Lechon, M. Jose
CORPORATE SOURCE: Unidad de Hepatologia Experimental, Centro de Investigacion, Hospital Universitario La Fe, Valencia, Spain
SOURCE: Drug Metabolism and Disposition (2005), 33(1), 108-114
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Suitability of human liver grafts preserved in Celsior solution (CS) for preparing metabolically competent hepatocyte cultures was examined To this end, basal and induced activity and mRNA levels of major hepatic cytochrome P 450 (P 450) enzymes were measured. By 24 h in culture, measurable levels of the 10 P 450 mRNAs studied were found in all hepatocyte prepns. examined, with CYP2E1, CYP2C9, and CYP3A4 mRNAs being the most abundant. Compared with hepatocytes obtained from surgical liver resections (SLRs), lower content of each P 450 mRNA was found in hepatocytes from the CS group; however, the relative distribution of individual P 450 mRNAs was similar. Similar results were observed after measuring P 450 activities. CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 activities in hepatocytes from CS-flushed grafts were lower than but comparable with those of cultures prepared from SLRs. No differences in the metabolite profile of testosterone were found. Treatment of hepatocytes from CS-preserved grafts with model P 450 inducers shows that 2 μM methylcholanthrene only increased CYP1A1 and CYP1A2 mRNAs (> 100-fold over control), 1 mM phenobarbital markedly increased CYP2A6, CYP2B6, and CYP3A4 mRNA content (> 7-fold), and 50 μM rifampicin highly increased CYP3A4 mRNA levels (> 10-fold), whereas minor effects (<3-fold) were observed in CYP2A6, CYP2B6, and CYP2C9 mRNAs. This induction pattern of P450s was similar, in terms of magnitude, reproducibility, and specificity, to that shown in primary hepatocytes from surgical biopsies. Overall, the authors' results indicate that, cold-preserved in CS, liver grafts constitute a valuable source of human hepatocytes for drug metabolism studies.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

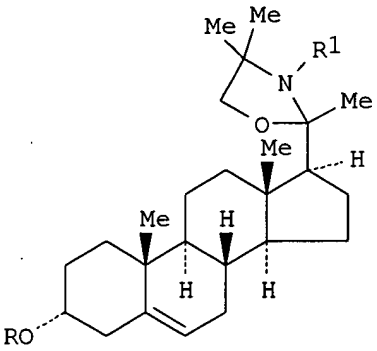
L16 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:370947 CAPLUS
DOCUMENT NUMBER: 140:391399
TITLE: Preparation of steroids comprising superoxide dismutase mimic groups and nitric oxide donor groups for therapeutic use in pharmaceutical compositions
INVENTOR(S): Haj-Yehia, Abdullah Ibrahim
PATENT ASSIGNEE(S): Yissum Research Development Company of the Hebrew University of Jerusalem, Israel
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037843	A2	20040506	WO 2003-IL878	20031024
WO 2004037843	A3	20040610		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003278565	A1	20040513	AU 2003-278565	20031024
EP 1562975	A2	20050817	EP 2003-769864	20031024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-421272P P 20021025
WO 2003-IL878 W 20031024

OTHER SOURCE(S): MARPAT 140:391399
GI



I

AB This invention relates to methods and devices for administering and to the preparation of multifunctional nitrato-DOXYL-steroids, of the general form R-(ONO2)n [R = steroid containing a heterocyclic nitrogen bonded oxyl radical; n = 1, 2, 3, etc.] combining a steroid component with SOD mimic component and optionally also with a NO donor component, for therapeutic use in treating and preventing disorders associated with oxidative stress and free radical injury, or disorders in which treatment with steroids is indicated, whereas such combination increases the efficacy of treatment and reduces side effects associated with steroid treatment and for treating disorders in which treatment with a smooth muscle relaxant is indicated. The prepared DOXYL-steroids were claimed for use in treating or preventing a disorder selected from the group consisting of respiratory, pulmonary, cardiovascular, inflammatory, and autoimmune disorders. These disorders include asthma, chronic bronchitis, bronchiectasis, bronchospasms, emphysema, chronic obstructive pulmonary diseases (COPD5), bronchial hyperreactivity, respiratory distress syndrome or chronic obstructive airway disease (COAD5), allergic conditions, arthritis, autoimmune hematol. disorders, systemic lupus erythematosus, systemic dermatomyositis, thrombocytopenia, psoriasis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, acne, hirsutism, erythema nodosum,

inflamed cysts, discoid lupus, bullous diseases, collagen vascular diseases, malignancies, neoplastic disease, trauma, shock, acute and chronic inflammatory conditions, sarcoidosis, Sweet's disease, graft-vs.-host disease, multiple sclerosis, Alzheimer's diseases, Parkinson's diseases, amyotrophic lateral sclerosis, convulsive disorders, AIDS-dementia, and disorders related to learning. Also, included are disorders related to olfaction, disorders related to nociception, cerebral edema, migraine, ophthalmic disorders, chronic adrenal insufficiency, congenital adrenal hyperplasia, gastrointestinal diseases, hepatic diseases, inflammatory bowel disease, Crohn's disease, ulcerative colitis, renal disease, gastric secretory and peristaltic functions, drug and disease-induced neuropathies and nephropathies, pathol. uterine contractions, sinus tachycardia, ischemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, atherosclerosis, rheumatic disorders, hypertension, arrhythmia, hyperthyroidism, cellular defense impairment, hypercholestemia, Reaven's Syndrome, vasculitis, arteritis, endothelial dysfunction-induced diseases, diabetes mellitus, insulin-resistance and glucose intolerance in diabetes, ischemia-reperfusion tissue injury, chemotaxis and phagocytic impairment in immunol. disorders, aging-mediated changes, cerebrovascular diseases, thyrotoxicosis, aggregation disorders, fertility conditions and reproductive disorders, menopause, ovarian dysfunction, testicular dysfunction, and penile erection. Thus, nitrato-DOXYL-steroid I (R = NO2, R1 = O.) was prepared via a synthetic sequence which included cyclization of pregnenolone with 2-amino-2-methylpropanol by refluxing 24 h using PTSA to form steroidal oxazolidine I (R = R1 = H) in 92% yield, oxidation of the steroidal oxazolidine with Na2WO4, H2O2 and EDTA at rt for 5 days to give DOXYL-steroidal alc. I (R = H, R1 = O.) in 84% yield, and finally, treatment of the DOXYL-steroidal alc. with N2O4 gas in THF and Et2O at rt for 10-24 h to give the target nitrato-DOXYL-steroid in 98% yield. The DOXYL-steroids were assayed in vitro using a model of biol. response for asthma for relaxation of tracheal rings from guinea pigs.

L16 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:149892 CAPLUS
DOCUMENT NUMBER: 140:418122
TITLE: Subnormal androgen levels in young female bone marrow transplant recipients with ovarian dysfunction, chronic GVHD and receiving glucocorticoid therapy
AUTHOR(S): Hovi, L.; Saarinen-Pihkala, U. M.; Taskinen, M.; Wikstroem, A. M.; Dunkel, L.
CORPORATE SOURCE: Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland
SOURCE: Bone Marrow Transplantation (2004), 33(5), 503-508
CODEN: BMTRE9; ISSN: 0268-3369
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ovarian function and sex hormone production with special focus on androgens (testosterone, androstenedione, dehydroepiandrosterone and its sulfate, DHEAS) was followed up during 1.5-20 (mean 9) years after bone marrow transplantation (BMT) in 24 female subjects aged 16-33 (mean 21) years at the last follow-up. All patients had received TBI and high-dose chemotherapy as the preparative regimen. A total of 24 female patients with conventionally treated pediatric hematol. malignancies served as controls. Four of 24 transplanted patients had spontaneous menstruation several years post transplantation, but in only one of them were serum FSH levels normal. Androgen levels of the BMT patients were lower than those of the conventionally treated patients. Subnormal testosterone levels were observed in 43% of BMT patients and subnormal DHEAS levels in 34% of BMT patients, the latter being a constant finding during glucocorticoid therapy for chronic GVHD (cGVHD). These results indicate that ovarian damage is a common late effect in patients transplanted at a young age, still having a

seemingly normal pubertal development. Ovarian damage and cGVHD with glucocorticoid therapy are strongly associated with subnormal androgen levels. The clin. consequences of these changes and possible benefits of putative androgen replacement therapy remain to be elucidated.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:653221 CAPLUS
DOCUMENT NUMBER: 125:266048
TITLE: Method of treating steroid-induced adenosine depletion
INVENTOR(S): Nyce, Jonathan W.
PATENT ASSIGNEE(S): East Carolina University, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9625935	A1	19960829	WO 1996-US1933	19960215
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG				
US 5660835	A	19970826	US 1995-393863	19950224
CA 2213339	C	19960829	CA 1996-2213339	19960215
CA 2213339	AA	19960829		
AU 9648677	A1	19960911	AU 1996-48677	19960215
AU 699917	B2	19981217		
EP 810863	A1	19971210	EP 1996-904622	19960215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
CN 1175903	A	19980311	CN 1996-192096	19960215
JP 11501620	T2	19990209	JP 1996-525728	19960215
JP 3725158	B2	20051207		
SG 79237	A1	20010320	SG 1998-3281	19960215
NZ 302592	A	20010928	NZ 1996-302592	19960215
EP 1555025	A2	20050720	EP 2005-4694	19960215
EP 1555025	A3	20050803		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AU 9911317	A1	19990304	AU 1999-11317	19990114
AU 730453	B2	20010308		
JP 2005306880	A2	20051104	JP 2005-162494	20050602

PRIORITY APPLN. INFO.:

US 1995-393863	A	19950224
AU 1996-48677	A3	19960215
EP 1996-904622	A3	19960215
JP 1996-525728	A3	19960215
WO 1996-US1933	W	19960215

OTHER SOURCE(S): MARPAT 125:266048

AB A method of treating adenosine depletion comprises administering to the subject in need folinic acid or a pharmaceutically acceptable salt thereof. Also, a method of treating asthma is disclosed comprising administering to the subject in need dehydroepiandrosterone (DHEA), analogs thereof, or pharmaceutically acceptable salts thereof. Rats administered DHEA (300 mg/kg) or methyltestosterone (MT) (120 mg/kg) daily for 2 wk showed multi-organ depletion of adenosine. Depletion was dramatic in brain (60 and 34% depletion for DHEA and MT, resp.) and heart (37 and 22% for DHEA and MT, resp.). Coadministration of folinic acid (50 mg/kg) completely abrogated steroid-mediated adenosine depletion. Folinic acid administered alone induced increases in adenosine levels for all

organs studied.

L16 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:622919 CAPLUS
DOCUMENT NUMBER: 121:222919
TITLE: Overexpression of a human transforming growth factor-α (TGFα) transgene reveals a dual antagonistic role of TGFα in female sexual development
AUTHOR(S): Ma, Ying Jun; Dissen, Gregory A.; Merlino, Glenn; Coquelin, Arthur; Ojeda, Sergio R.
CORPORATE SOURCE: Div. Neuroscience, Oregon Regional Primate Research Center, Beaverton, OR, 97006, USA
SOURCE: Endocrinology (1994), 135(4), 1392-400
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The importance of transforming growth factor-α (TGFα) in female reproductive development was assessed using transgenic mice bearing a human TGFα complementary DNA under the control of a mouse metallothionein-1 promoter (MT1-hTGFα). Examination of the brain and ovaries 5 h after a single s.c. injection of ZnCl2, administered to activate the MT1-hTGFα transgene, revealed that prominent sites of human TGFα mRNA expression within these tissues were the hypothalamus and ovarian follicles, resp. In vitro expts. showed that acute transgene activation increased hypothalamic release of LH-RH. In contrast, the ovarian steroidal response to gonadotropins, examined in vitro, was markedly attenuated. Chronic activation of transgene expression by daily administration of ZnCl2 delayed the time of first estrus (an index of peripubertal estrogen secretion), but shortened the interval between first estrus and the onset of estrous cyclicity (an index of reproductive competence). Accumulation of small antral follicles, accompanied by thecal hypertrophy and enhanced androgen production, preceded the acquisition of ovulatory capacity. These changes were accompanied by reduced serum LH levels, suggesting that the relative inability of small antral follicles to develop further in TGFα-overexpressing mice is at least in part due to inappropriate gonadotropin support. Serum LH levels in these animals may be reduced by an augmented androgen neg. feedback signal. Nontransgenic mouse ovaries, placed under the control of a transgenic hypothalamus by heterologous grafting, rapidly ovulated and initiated estrous cyclicity. In contrast, acquisition of reproductive capacity was severely delayed in nontransgenic mice bearing transgenic ovarian grafts. The results indicate that TGFα regulates female reproductive development through two opposing mechanisms: within the brain, it facilitates the neuroendocrine activation of the process; at the ovarian level, it modulates the stimulatory effect of gonadotropin hormones on follicular growth and steroidogenesis.

L16 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:624308 CAPLUS
DOCUMENT NUMBER: 113:224308
TITLE: Greater conversion of testosterone to 5α-dihydrotestosterone, reflecting increased peripheral 5α-reductase activity in nude mice treated with high doses of cyclosporin A
AUTHOR(S): Boudou, Philippe; Fiet, Jean; Vexiau, Patrick; Villette, Jean Marie; Hardy, Noah; Dreux, Claude
CORPORATE SOURCE: Horm. Biol. Lab., Hop. Saint-Louis, Paris, 75010, Fr.
SOURCE: Journal of Steroid Biochemistry (1990), 36(6), 597-601
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following cyclosporin A (CsA) immunosuppressive therapy in kidney

grafts, increased body hair growth (hypertrichosis and/or hirsutism) without significant variation in normal circulating plasma androgen levels (as observed in idiopathic hirsutism) has been reported by several authors. Other authors have described increased hair growth in nude mice treated with CsA. In order to evaluate the action of this drug in target tissues, using dorsal skin homogenates from nude mice treated with various doses of CsA, the metabolic conversion of testosterone (T) to its 5α-reduced products was determined, reflecting 5α-reductase activity (5α-RA). Three groups of 5 female nude mice were treated with an oral suspension containing CsA 5 (group 1), 25 (group 2) and 100 mg/kg (group 3), resp., and the results, including 5α-DHT (dihydrotestosterone) and Adiol formation, were compared with those obtained in a control group receiving only the olive oil vehicle. Cutaneous metabolic conversion of T was determined using tritiated T as substrate. After 1 h of incubation, 5α-DHT and other 5α-reduced products formed were separated and quantified using a reverse-phase chromatog. column fitted to a flow-through radioactivity detector. Mean 5α-DHT formation (expressed as pmol per 100 mg of protein per h) was increased in the treated groups (group 1: 3.17, group 2: 3.10, group 3: 4.26), higher than in the control group (2.95). In addition to 5α-DHT, enhanced formation of Δ4-androstenedione (Δ4), 5α- androstan -3β,17β-diol (2β-diol) and adiol were also observed in the treated groups. These results show a significantly increased formation of 5α-DHT (and adiol) in nude mice treated with high dose-levels of CsA.

L16 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:546996 CAPLUS
DOCUMENT NUMBER: 111:146996
TITLE: Anti-allergic action of glucocorticoids. II. Effect of glucocorticoids on cell mediated (Type IV) allergic reactions
AUTHOR(S): Nagai, Hiroichi; Takizawa, Tamotsu; Inagaki, Naoki; Sakamoto, Tatsuo; Shimazawa, Tsukasa; Koda, Akihide
CORPORATE SOURCE: Dep. Pharmacol., Gifu Pharm. Univ., Gifu, 501-21, Japan
SOURCE: Arerugi (1989), 38(6), 493-500
CODEN: ARERAM; ISSN: 0021-4884
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of 3 glucocorticoids (hydrocortisone, prednisolone, and dexamethasone) on cell-mediated hypersensitivity (type IV allergy) reactions were examined in rats and mice. These steroids inhibited both the induction and the effector phases of type IV reaction induced by sheep red blood cells (SRBC) in mouse footpads. The local graft vs. host reaction induced by lymphocytes from Brown Norway rats in the footpads of (Lewis X Brown Norway) F1 rats was also clearly inhibited by the steroids. The inhibitory action of the steroids on footpad reactions induced by SRBC was prevented by pretreatment with non-corticoid steroids (17α-methyltestosterone, androsterone, and progesterone). Release of lymphokines, macrophage chemotactic factor (MCF) and skin reactive factor (SRF) was inhibited by each steroid at a high concentration Moreover, the steroids inhibited the activity of MCF in vitro and of SRF in vivo.

L16 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:161800 CAPLUS
DOCUMENT NUMBER: 108:161800
TITLE: Growth hormone modifies the growth rate of enzyme-altered hepatic foci in male rats treated according to the resistant hepatocyte model
AUTHOR(S): Blanck, Agneta; Hansson, Tiiu; Eriksson, Lennart C.;

Gustafsson, Jan Aake
CORPORATE SOURCE: Karolinska Inst., Huddinge Univ. Hosp., Huddinge, S-141 86, Swed.
SOURCE: Carcinogenesis (1987), 8(11), 1585-8
CODEN: CRNGDP; ISSN: 0143-3334
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Male and female Wistar rats were given an initiating i.p. injection of diethylnitrosamine (200 mg/kg). Two weeks later the rats were given a diet containing 0.02% 2-acetylaminofluorene (2-AAF) for 2 wk. In the middle of the 2-AAF treatment a 70% partial hepatectomy (PH) was performed. To identify the pituitary hormone responsible for the previously observed sex difference (male > female) in, and the influence of ectopic pituitary grafts on focal growth during 2-AAF/PH selection of enzyme-altered foci, male rats were treated with a continuous infusion of bovine growth hormone (bGH; 6 μg/h) or ovine prolactin (oPrl; 6 μg/h) using osmotic minipumps. Hormone treatment was started 1 wk after initiation and was finished 1 wk after the 2-AAF selection period. All rats were killed 6 wk after initiation and liver sections were stained for γ-glutamyltransferase. The number of foci/cm2 as well as the area per focus and area ratio (mm2 foci/cm2 liver section) were calculated No differences in the number of foci/cm2 were observed between the different groups of rats, but bGH treatment of male rats decreased both the area/focus and the area ratio down to the female level. No effects were seen following oPrl administration when compared with control males. In vitro studies of subcellular prepns. from the liver lobes obtained at PH showed that the sexually differentiated N-hydroxy-2-AAF sulfotransferase activity (male > female) in male rats was feminized, i.e. decreased, by bGH administration, but not by oPrl infusion. This strengthened the view of growth hormone as an important determinant of sex differences in chemical carcinogenesis in rat liver, possibly via an influence on carcinogen metabolism

L16 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:491704 CAPLUS
DOCUMENT NUMBER: 105:91704
TITLE: Hyperprolactinemia enhances LH-stimulated 4-ene-5α-reductase activity but inhibits LH-induced 17-hydroxylase activity in testes of hypophysectomized immature rats
AUTHOR(S): Nagareda, T.; Takeyama, M.; Ueda, T.; Koizumi, K.; Namiki, M.; Okuyama, A.; Matsumoto, K.
CORPORATE SOURCE: Med. Sch., Osaka Univ., Osaka, 530, Japan
SOURCE: Journal of Steroid Biochemistry (1986), 24(6), 1199-204
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two pituitaries from 7-wk-old female rats were grafted under the capsule of the left kidney of 21-day-old male rats and the pituitary-grafted and sham-operated rats were hypophysectomized at 27 days of age. The hypophysectomized rats, were given daily injections of 9 μg NIAMDD-ovine LH-23 (min. ED) or saline for 3 days starting from day 29. Testicular homogenates were incubated with 3H-labeled progesterone [57-83-0] or 14C-labeled 4-androstene-3,17-dione [63-05-8], and enzyme activities per testis were estimated Testicular human chorionic gonadotropin [9002-61-3] binding sites were also measured. Hypophysectomy caused decreases in activities of testicular 5α-reductase [9036-43-5], steroid 17-hydroxylase [9029-67-8], and 17β-hydroxysteroid oxidoreductase [9015-81-0]. These decreased enzyme activities were stimulated by LH [9002-67-9] treatment. Although pituitary grafts alone showed no effects on these enzyme activities in the testes of the hypophysectomized rats, the grafts

enhanced LH-stimulated 5α-reductase activities but inhibited LH-stimulated 17-hydroxylase activity. Testicular LH-HCG receptors were increased by the grafts, especially in the presence of LH, without affecting affinity for HCG. Thus, hyperprolactinemia directly stimulated LH-stimulated 5α-reductase activity in rat testes. The same grafts also directly inhibit LH-stimulated 17-hydroxylase activity, probably via postreceptor mechanisms.

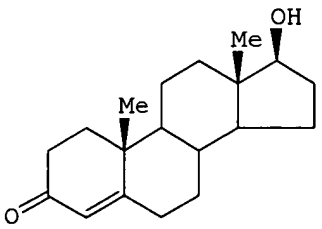
L16 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:435937 CAPLUS
DOCUMENT NUMBER: 105:35937
TITLE: Stimulatory effect of prolactin on luteinizing hormone-induced testicular 5α-reductase activity in hypophysectomized adult rats
AUTHOR(S): Takeyama, M.; Nagareda, T.; Takatsuka, D.; Namiki, M.; Koizumi, K.; Aono, T.; Matsumoto, K.
CORPORATE SOURCE: Med. Sch., Osaka Univ., Osaka, 530, Japan
SOURCE: Endocrinology (1986), 118(6), 2268-75
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two pituitaries from 7-wk-old female rats were grafted under the capsule of the left kidney of 50-day-old male rat to induce hyperprolactinemia. All of the pituitary-grafted and sham-operated rats were hypophysectomized at 56 days of age. The hypophysectomized rats in groups of 4 were given daily s.c. injections of saline or 9 μg NIADDK-ovine-(o)LH-23 for 4 and 5 days starting from days 58 and 70, resp. (short- and long-term hypophysectomized groups). The metabolism of 3H-labeled progesterone [57-83-0] or 14C-labeled androstenedione [63-05-8] by testicular homogenates, concns. of testosterone [58-22-0] and 5α-androgens (androsterone [53-41-8] plus 5α-androstane-3α,17β-diol [1852-53-5]) in the serum and testes, and testicular LH [9002-67-9] receptors were estimated Hypophysectomy caused significant decreases in testicular enzyme activities, androgen production, and testicular LH receptors. In the testes of hypophysectomized rats, LH treatment significantly stimulated 5α-reductase [9036-43-5] and 17-hydroxylase [9046-59-7] activities. Although pituitary grafts alone showed little or no effect on these testicular enzyme activities, hyperprolactinemia induced by the grafts markedly enhanced the LH-stimulated 5α-reductase activity in both groups, especially in the long-term hypophysectomized group. Therefore, androsterone and 5α-androstane-3α,17β-diol were shown to be the major C19-steroid products (immature type of testicular androgen production) in the LH- and prolactin (PRL) [9002-62-4]-stimulated testes of long-term hypophysectomized adult rats. On the other hand, hyperprolactinemia was associated with a significant inhibition and a slight increase of the LH-stimulated 17-hydroxylase activities in the short- and long-term hypophysectomized groups, resp. This difference can be attributed to both a PRL-induced increase in testicular LH receptors and a PRL-induced inhibition of 17-hydroxylase via a postreceptor mechanism(s). Apparently, PRL directly stimulates LH-induced 5α-reductase activity in the testes. PRL may play a role in the increased production of 5α-C19-steroids and the parallel decrease of testosterone production in immature rat testes.

L16 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:516630 CAPLUS
DOCUMENT NUMBER: 103:116630
TITLE: Effects of hyperprolactinemia on activities of 17-hydroxylase, 17β-ol-dehydrogenase and 5α-reductase in neonatally grafted and host testes in mice

AUTHOR(S): Takeyama, M.; Nagareda, T.; Takatsuka, D.; Uchida, K.; Wakabayashi, K.; Matsumoto, K.
CORPORATE SOURCE: Med. Sch., Osaka Univ., Osaka, 530, Japan
SOURCE: Journal of Steroid Biochemistry (1985), 22(6), 837-42
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Male and female (WB + C57BL/6)F1 hybrid mice were used. Two pituitaries from 60-80-day-old female mice were grafted under the capsule of the left kidney of 60-80-day-old male mice. One week after grafting, 2 testes from neonatal mice were grafted under the capsule of the right kidney of the grafted mice and 70-90-day-old intact male mice. The grafted and host testes, in groups of 10-26, were removed 15-120 days after transplantation of the neonatal testes. Testicular homogenates were incubated with 3H-labeled progesterone [57-83-0] or 14C-labeled 4-androstene-3,17-dione [63-05-8], and enzyme activities per g tissue were estimated Elevated prolactin [9002-62-4] levels, slightly lower LH levels, and normal testosterone levels were found in the mice with pituitary grafts, compared with those in the mice without pituitary grafts. Activities of 17-hydroxylase (I) [84419-07-8] and 17β-ol dehydrogenase (II) [9015-81-0] increased clearly with age in the grafted testes in the mice without pituitary grafts, though the increases were inhibited by the pituitary grafts. However, the pituitary grafts had no effect on activities of I and II in the host testes under similar gonadotropic stimulation. 5α-Reductase [9036-43-5] activities in the grafted and host testes were unaffected by the pituitary grafts. Thus hyperprolactinemia may thus directly inhibit increases in activities of I and II with testicular age in neonatally grafted tests in mice.

L16 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:516347 CAPLUS
DOCUMENT NUMBER: 99:116347
TITLE: Prenatal testosterone propionate and postnatal ovarian activity in the rat
AUTHOR(S): Koos Slob, A.; Den Hamer, R.; Woutersen, P. J. A.; Van der Werff ten Bosch, J. J.
CORPORATE SOURCE: Fac. Med., Erasmus Univ., Rotterdam, 3000 DR, Neth.
SOURCE: Acta Endocrinologica (1983), 103(3), 420-7
CODEN: ACENA7; ISSN: 0001-5598
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

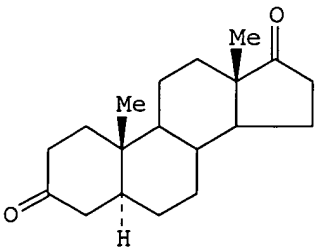


I

AB Testosterone (I) [58-22-0] was given to rats on days 16 through 20 of pregnancy (2 mg I propionate/day). Female young had masculinized external genitalia. Sexual maturity was accelerated in I females, despite lower wts. and shorter lengths of body and tail. Placental and body wts. were lower in I females and males than in controls. The inhibiting effect of I on postnatal growth is probably mediated by its effect on birth weight through placental damage. Ovarian cyclicity occurred on reaching sexual

maturity. In 1 experiment, I females were ovariectomized at 6 wk and given ovarian and vaginal grafts. Most of these animals showed regular cyclicity in vaginal smears between 74 and 100 days. Thus, neither the early nor the delayed early androgen syndrome occurred in these expts. This absence of effect of prenatal I on ovarian cyclicity is attributable to a placental barrier for I. When maternal plasma I was raised 20-fold by exogenous I, fetal I levels remained unchanged. More detailed information was obtained when labeled I was infused into a pregnant rat. I did not reach the fetus as such, but mainly as androsterone [53-41-8], which cannot be converted into estrogens. This explains why prenatal I can cause masculinization of genitalia, without masculinizing the gonadotropin secretion pattern in female rats. The latter process would presumably require estrogenic compds.

L16 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1978:164722 CAPLUS
DOCUMENT NUMBER: 88:164722
TITLE: Failure of inhibiting corneal graft rejection in rabbits by 5α- androstane -3,17-dione
AUTHOR(S): Niederer, Werner; Eltz, Heinz
CORPORATE SOURCE: Dep. Ophthalmol., Univ. Basel, Basel, Switz.
SOURCE: Ophthalmologica (1978), 176(1), 45-51
CODEN: OPHTAD; ISSN: 0030-3755
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB In rabbits immunized with residual corneal tissue from donor eyes, 5α- androstane-3,17-dione (I) [846-46-8] (2% ointment) did not inhibit corneal graft rejection as effectively as did cortisol [50-23-7]. Some histol. features of corneal graft rejection and the technique of corneal grafting in rabbits are discussed.

L16 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:436430 CAPLUS
DOCUMENT NUMBER: 87:36430
TITLE: The effects on hepatic steroid metabolism of an ectopic pituitary graft: a time study
AUTHOR(S): Eneroth, Peter; Gustafsson, Jan Ake; Skett, Paul; Stenberg, Ake
CORPORATE SOURCE: Hormonlab., Karolinska Sjukhuset, Stockholm, Swed.
SOURCE: Molecular and Cellular Endocrinology (1977), 7(2), 167-75
CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The time course of feminization of hepatic steroid metabolism in the rat was followed after transplantation of a normal male or female pituitary gland

under the kidney capsule of the host animal. Feminization of enzymes active on 4-androstene-3,17-dione and 5α-androstane-3α,17β-diol occurred between 4 and 8 days after transplantation. Prior to this, masculinization of liver enzyme activities was observed in the transplanted animals. Only prolactin was produced by the ectopic pituitary gland. A lag period of 2-4 days was observed before prolactin appeared in host serum. The serum concns. of prolactin, LH and FSH were poorly correlated with the degree of feminization of hepatic steroid metabolism in the host animal. Apparently, the ectopic pituitary gland within 4-8 days after implantation begins to secrete factor(s) which is (are) not identical to prolactin LH, and FSH, and which feminize(s) the steroid metabolism in the liver.

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=> s l21 and amino
       1079432 AMINO
            43 AMINOS
       1079449 AMINO
                 (AMINO OR AMINOS)
L22       4292 L21 AND AMINO

=> s l22 and androst?
         32608 ANDROST?
L23        321 L22 AND ANDROST?

=> s l23 and hydroxy
        441958 HYDROXY
            11 HYDROXIES
        441969 HYDROXY
                 (HYDROXY OR HYDROXIES)
L24        103 L23 AND HYDROXY

=> s l2 and (immune? or immuno? or transplant? or graft? or liver failure or kidney
failure)
             0 L2
        200635 IMMUNE?
        793840 IMMUNO?
         55746 IG
         14848 IGS
         63240 IG
                 (IG OR IGS)
        811744 IMMUNO?
                 (IMMUNO? OR IG)
         95911 TRANSPLANT?
        129813 GRAFT?
        543700 LIVER
         36005 LIVERS
        546686 LIVER
                 (LIVER OR LIVERS)
        183209 FAILURE
         15704 FAILURES
        193112 FAILURE
                 (FAILURE OR FAILURES)
          2451 LIVER FAILURE
                 (LIVER(W)FAILURE)
        281241 KIDNEY
         65969 KIDNEYS
        302136 KIDNEY
                 (KIDNEY OR KIDNEYS)
        183209 FAILURE
         15704 FAILURES
        193112 FAILURE
                 (FAILURE OR FAILURES)
          6368 KIDNEY FAILURE
                 (KIDNEY(W)FAILURE)
L25          0 L2 AND (IMMUNE? OR IMMUNO? OR TRANSPLANT? OR GRAFT? OR LIVER
               FAILURE OR KIDNEY FAILURE)

=> focus
PROCESSING COMPLETED FOR L24
L26        103 FOCUS L24 1-

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L26  ANSWER 1 OF 103  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        1960:34472  CAPLUS
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DOCUMENT NUMBER: 54:34472
ORIGINAL REFERENCE NO.: 54:6826h-i,6827a-c
TITLE: Enzymic synthesis of aryl sulfamates
AUTHOR(S): Roy, A. B.
CORPORATE SOURCE: Univ. Edinburgh, UK
SOURCE: Biochemical Journal (1960), 74, 49-56
CODEN: BIJOAK; ISSN: 0264-6021
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. ibid. 63, 294(1956). The determination of sulfamate (I) for the assay of I synthesis by liver prepns. is based on the removal of free amino compds. by treatment with ion-exchange resin, hydrolysis of the sulfamate by HCl to the amino compound and its subsequent determination by diazotization in NaNO2 and NaOH and coupling with thymol. The intensity of the resulting color is determined The pH optimum of the enzyme reaction is 8.2, the optimum concentration of adenosinetriphosphate 4 mM, the optimum sulfate concentration 10 mM, and the optimum concentration of 2-naphthylamine >2 mM. 1-Naphthylamine and aniline are also substrates for this enzyme system, but benzylamine and glucosamine are not. I is probably formed by the transfer of sulfate from adenosine-3'-phosphate-5'-sulfatophosphate, the transfer being catalyzed by arylamine sulfatase, which has an optimum pH of 8.2 and requires the presence of at least 2 mM Mg2+ ions before it shows its activity. The enzyme is inhibited by p-chloromercuribenzoate and the inhibition is abolished by cysteine. The rate of synthesis of 2-naphthyl sulfamate by rat-liver prepns. is increased by about 400% by 17-keto steroids in concns. of approx. 10-5M. The rate of synthesis of I by guinea pig prepns. is not increased by 17-keto steroids. It is suggested that the mechanism of this activation involves the formation of steroid 17-enol sulfates and that these enol sulfates would be a form of active sulfate, having a high sulfate-group potential. The following steroids have been studied: 3-hydroxyestra-1,3,5-triene, -trien-16-one and -17-one, 3-methoxyestra-1,3,5-trien-17-one, 3,16α-dihydroxyestra-1,3,5-trien-17-one, 3β- hydroxy-5α- androstan -17-one, 3β- hydroxy-5α- androstan-17-one, 3α- hydroxy-5β- androstan-17-one, 3β- hydroxy-5β- androstan-17-one, 3β-hydroxyandrost-5-en-17-one, 3β-acetoxyandrost-5-en-17-one, 3β-methoxyandrost-5-en-17-one, 3β,16β-epiandrostan-17-one, dihydroxyandrost-5-en-17-one, 6β- hydroxy-3,5-17α- and 17β-hydroxyandrost-4-en-3-one, 3β,17β-dihydroxyandrost-4-one, androst -4-ene-3,11,17-trione, 3α- and 3β- hydroxy -5α-pregnan-20-one, 3α- and 3β- hydroxy -5β-pregnan-20-one, 3β-hydroxypregn-5-en-20-one, 17α,21-dihydroxypregn-4-ene-3,11,20-trione, and 11β,17α,21-trihydroxypregn-4-ene-3,20-dione. The rates of synthesis of p-nitrophenyl sulfate, estrone sulfate, dehydroepiandrosterone sulfate, epitestosterone sulfate and 2-naphthyl sulfamate have been determined
IT Steroids
(17-keto-, effect on formation of aryl sulfamates by enzymes of liver)
IT Liver
(aryl sulfamate formation by enzymes of)
IT Sulfamates
(formation of aryl, by enzymes of liver and their determination)
IT 53-41-8, Androsterone 1224-92-6, 5α- Androstan -3β-ol 1476-64-8, Androst-5-en-3β-ol
(effect on formation of aryl sulfamates by enzymes)
IT 53-06-5, Cortisone 53-42-9, 5β- Androstan-17-one, 3α- hydroxy- 53-43-0, Androst-5-en-17-one, 3β- hydroxy- 53-63-4, Estra-1,3,5(10)-trien-3-ol 128-20-1, 5β-Pregnan-20-one, 3α- hydroxy- 128-21-2, 5β-Pregnan-20-one, 3β- hydroxy- 145-13-1,

Pregn-5-en-20-one, 3β- hydroxy- 382-45-6, Androst
-4-ene-3,11,17-trione 481-29-8, 5α- Androstan-17-one,
3β- hydroxy- 481-30-1, Androst-4-en-3-one,
17α- hydroxy- 481-97-0, Estrone, sulfate 516-54-1,
5α-Pregnan-20-one, 3α- hydroxy- 516-55-2,
5α-Pregnan-20-one, 3β- hydroxy- 566-76-7,
Estra-1,3,5(10)-trien-17-one, 3,16α-dihydroxy- 571-31-3, 5β-
Androstan-17-one, 3β- hydroxy- 1156-92-9,
Androst-4-ene-3β,17β-diol 1624-62-0,
Estra-1,3,5(10)-trien-17-one, 3-methoxy- 4579-56-0, Androst
-4-en-3-one, 17α- hydroxy-, hydrogen sulfate 10457-69-9,
Androst-5-en-17-one, 3β-methoxy-
(effect on formation of aryl sulfamates by enzymes of liver)

IT 382-44-5, Androst-4-ene-3,17-dione, 11β- hydroxy-
663-39-8, 3,5-Cyclo-5α- androstan-17-one, 6β-
hydroxy-
(effect on formation of aryl sulfamates by liver)

IT 1159-68-8, Androst-5-en-17-one, 3β,16β-dihydroxy-
(effect on formation of aryl sulfamates by liver enzymes)

IT 3601-97-6, Estra-1,3,5(10)-trien-16-one, 3-hydroxy-
(effet on formation of aryl sulfamates by enzymes of liver)

IT 53-43-0, Androst-5-en-17-one, 3β- hydroxy-
(esters, effect on formation of aryl sulfamates by enzymes of liver)

IT 1080-04-2, Phenol, p-nitro-, hydrogen sulfate
(formation by liver)

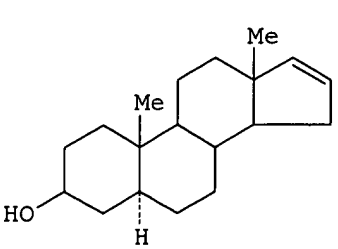
IT 10345-06-9, 2-Naphthalenesulfamic acid
(formation by liver enzymes)

IT 9068-67-1, Sulfatase
(formation of aryl sulfamates by)

IT 50-23-7, Cortisol
(in aryl sulfamate formation by enzymes of liver)

IT 58-22-0, Testosterone 63-05-8, Androst
-4-ene-3,17-dione
(in aryl sulfamate formation by liver)

L26 ANSWER 2 OF 103 CAPLUS 'COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:22138 CAPLUS
DOCUMENT NUMBER: 108:22138
TITLE: Synthesis of four stereoisomeric 3β,17-dihydroxy-
16-amino-5α- androstanes
AUTHOR(S): Zhao, Ming; Liao, Qingjiang; Xiang, Manwen
CORPORATE SOURCE: Dep. Org. Chem., Nanjing Coll. Pharm., Nanjing, Peop.
Rep. China
SOURCE: Youji Huaxue (1987), (1), 34-40
CODEN: YCHHDX; ISSN: 0253-2786
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 108:22138
GI



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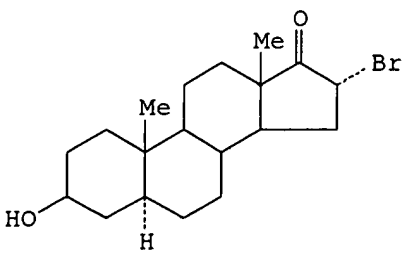

II

AB Starting from epiandrosterone, intermediates 3β- hydroxy -5α- androst-16-ene (I) and 3β- hydroxy -16α-bromo-5α- androst-17-one (II) were synthesized. 3β,17α-Dihydroxy-16α- amino-5α- androstane and its 16β- amino isomer were obtained from I; 3β, 17β-dihydroxy-16α- amino-5α- androstane and its 16β- amino isomer from II. The configurations of these four stereoisomers were confirmed via chemical conversions and spectral data.

IT 7148-51-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(epoxidn. of)

IT 41469-89-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and bromination of)

IT 111981-24-9P 111981-26-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and condensation of, with acetone)

IT 111981-25-0P 111981-27-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyclocondensation of, with acetone)

IT 111000-97-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and oxidation of)

IT 111058-55-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with sodium azide)

IT 111981-21-6P 111981-22-7P 111981-23-8P 112001-72-6P 112066-26-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)

IT 571-20-0P 5856-11-1P 111981-28-3P 111981-29-4P
111981-30-7P 111981-31-8P 111981-32-9P 111997-29-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT 85651-57-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium azide)

IT 481-29-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium hydride)

L26 ANSWER 3 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1966:84773 CAPLUS
DOCUMENT NUMBER: 64:84773
ORIGINAL REFERENCE NO.: 64:15944e-g
TITLE: Synthesis of derivatives of androstane series. VIII. Dihydrazones of androstane -3,17-dione and 4-androstene-3,17 -dione
AUTHOR(S): Volovel'skii, L. N.
SOURCE: Zhurnal Obshchei Khimii (1966), 36(2), 237-9
CODEN: ZOKHA4; ISSN: 0044-460X
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB cf. CA 51, 10553e; 63, 14934e. Heating the title diones with acid hydrazides gave the following bis(N-acylhydrazones): from 3,17-androstanedione (acyl group and m.p. shown): formyl, 282-5°; acetyl, 278-80°; propionyl, 259-61°; butyryl, 274-6°; caproyl, 253-5°; enanthoyl,

245-7°; stearoyl, 160-4°; benzoyl, 240-2°;
phenylacetyl, 255-7°; phenylpropionyl, 239-41°; cinnamoyl,
302-4°; α-methylcinnamoyl, 254-6°;
α-methylhydrocinnamoyl, 273-5°; anisoyl, 249-51°;
phenoxyacetyl, 175-7°; p-chlorophenoxyacetyl, 210-12°;
phenylethylacetyl, 275-7°; salicyloyl, 272-4°; anthraniloyl,
265-8°; p-aminobenzoyl, 318-21° p-aminosalicyloyl,
335-8°; cholanoyl, 210-12°; 3α-hydroxycholanoyl,
261-3°; 3α 6α-dihydroxycholanoyl, 250-2°;
3α,12°-dihydroxycholanoyl, 267-9°;
3α,7α-12α-trihydroxycholanoyl, 279-81°; 3α-
hydroxy-12α-methoxy-9(11)-cholenoyl, 263-5°;
3α- hydroxy-5-cholenoyl, 253-6°;
3α-hydroxyetio-5-cholenoyl, 177-9°; nicotinoyl,
237-9°; isonicotinoyl, 275-7°; from 4-androstene
-3,17-dione (same acyl groups as above, resp.): m. 340-2°; m.
333-5°; m. 306-8°; m. 327-9°; m. 273-5°; m.
276-8°; m. 201-4°; m. 278-80°; m. 275-7°; m.
267-9°; --; m. 268-9°; m. 279-81°; m. 260-2°;
m. 243-5°; m. 265-7°; m. 265-7°; m. 264-6°; m.
287-90°; m. 262-4°; m. 315-18°; m. 237-40°; m.
246-8°; m. 269-72°; m. 232-4°; m. 253-5; in.
229-32°; m. 283-5°; m. 156-8°; m. 282-4°; m.
293-6°.

IT Acetic acid, 5α- androstane-3,17-diylidenedihydrazide
Acetic acid, androst-4-ene-3,17-diylidenedihydrazide
Deoxycholic acid, 5α- androstane-3,17-divlidenedihvdrazide
Deoxycholic acid, androst-4-ene-3,17-divylidenedihvdrazide
Formic acid, 5α- androstane-3,17-diylidenedihydrazide
Formic acid, androst-4-ene-3,17-diylidenedihydrazide
Hexanoic acid, 5α- androstane-3,17-diylidenedihydrazide
Hexanoic acid, androst-4-ene-3,17-diylidenedihydrazide

IT 63-05-8, Androst-4-ene-3,17-dione
(bis(acylhydrazones))

IT 846-46-8, 5α- Androstane-3,17-dione, bis(acylhydrazones)
5696-61-7, Propionic acid, 5α- androstane
-3,17-diylidenedihydrazide 5696-62-8, Butyric acid, 5α-
androstane-3,17-diylidenedihydrazide 5696-64-0, Heptanoic acid,
5α- androstane-3,17-diylidenedihydrazide 5696-65-1,
Benzoic acid, 5α- androstane-3,17-diylidenedihydrazide
5696-66-2, Hydrocinnamic acid, 5α- androstane
-3,17-diylidenedihydrazide 5696-67-3, Cinnamic acid, 5α-
androstane-3,17-diylidenedihydrazide 5696-68-4, Cinnamic acid,
α-methyl-, 5α- androstane-3,17-diylidenedihydrazide
5708-21-4, p-Anisic acid, 5α- androstane
-3,17-diylidenedihydrazide 5708-22-5, Acetic acid, phenoxy-, 5α-
androstane-3,17-diylidenedihydrazide 5708-23-6, Acetic acid,
(p-chlorophenoxy)-, 5α- androstane-3,17-
diylidenedihydrazide 5708-25-8, Salicylic acid, 5α-
androstane-3,17-diylidenedihydrazide 5708-26-9, Anthranilic
acid, 5α- androstane-3,17-diylidenedihydrazide 5708-27-0,
Isonicotinic acid, 5α- androstane-3,17-diylidenedihydrazide
5708-30-5, Propionic acid, androst-4-ene-3,17-
diylidenedihydrazide 5708-31-6, Butyric acid, androst
-4-ene-3,17-diylidenedihydrazide 5708-33-8, Heptanoic acid,
androst-4-ene-3,17-diylidenedihydrazide 5708-34-9, Stearic acid,
androst-4-ene-3,17-diylidenedihydrazide 5708-35-0, Benzoic acid,
androst-4-ene-3,17-diylidenedihydrazide 5708-36-1, Hydrocinnamic
acid, androst-4-ene-3,17-diylidenedihydrazide 5708-37-2,
Cinnamic acid, α-methyl-, androst-4-ene-3,17-
diylidenedihydrazide 5708-38-3, Hydrocinnamic acid, α-methyl-,
androst-4-ene-3,17-diylidenedihydrazide 5708-39-4, p-Anisic
acid, androst-4-ene-3,17-diylidenedihydrazide 5708-41-8,

Salicylic acid, androst-4-ene-3,17-diylidenedihydrazide 5708-42-9, Anthranilic acid, androst-4-ene-3,17-diylidenedihydrazide 5708-43-0, Benzoic acid, p-amino-, androst-4-ene-3,17-diylidenedihydrazide 5708-44-1, Salicylic acid, 4-amino-, androst-4-ene-3,17-diylidenedihydrazide 5708-48-5, Nicotinic acid, androst-4-ene-3,17-diylidenedihydrazide 5708-49-6, Isonicotinic acid, androst-4-ene-3,17-diylidenedihydrazide 5748-99-2, Benzoic acid, p-amino-, 5α- androstane-3,17-diylidenedihydrazide 5749-01-9, Acetic acid, phenyl-, androst-4-ene-3,17-diylidenedihydrazide 6002-05-7, Nicotinic acid, 5α-androstane-3,17-diylidenedihydrazide 6057-68-7, Salicylic acid, 4-amino-, 5α- androstane-3,17-diylidenedihydrazide 6057-75-6, Androst-5-ene-17β-carboxylic acid, 3α- hydroxy-, 5α- androstane-3,17-diylidenedihydrazide 6072-39-5, Stearic acid, 5α-androstane-3,17-diylidenedihydrazide 6167-52-8, 5β-Cholanic acid, 3α- hydroxy-, 5α- androstane-3,17-diylidenedihydrazide 6167-53-9, 5β-Chol-9(11)-enic acid, 3α- hydroxy-12α-methoxy-, 5α- androstane-3,17-diylidenedihydrazide 6190-01-8, Acetic acid, phenoxy-, androst-4-ene-3,17-diylidenedihydrazide 6190-02-9, Acetic acid, (p-chlorophenoxy)-, androst-4-ene-3,17-diylidenedihydrazide 6193-50-6, Acetic acid, phenyl-, 5α- androstane-3,17-diylidenedihydrazide 6199-60-6, Cholic acid, 5α-androstane-3,17-diylidenedihydrazide 6199-61-7, Chol-5-enic acid, 3α- hydroxy-, 5α- androstane-3,17-diylidenedihydrazide 6363-94-6, Hydrocinnamic acid, α-methyl-, 5α- androstane-3,17-diylidenedihydrazide 6363-95-7, 5β-Cholanic acid, 3α,6α-dihydroxy-, 5α-androstane-3,17-diylidenedihydrazide 6400-01-7, 5β-Cholanic acid, 5α- androstane-3,17-diylidenedihydrazide 7192-85-0, Butyric acid, 2-phenyl-, androst-4-ene-3,17-diylidenedihydrazide 7322-18-1, Butyric acid, 2-phenyl-, 5α- androstane-3,17-diylidenedihydrazide
(preparation of)

L26 ANSWER 4 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:4493 CAPLUS
DOCUMENT NUMBER: 56:4493
ORIGINAL REFERENCE NO.: 56:858a
TITLE: Amino-aciduria and amino-acidemia in cirrhosis in the course of steroid treatment (Chromatographic research)
AUTHOR(S): Grassi, Bruno; Cagianelli, Mario A.; Pieri, Nada
CORPORATE SOURCE: Univ. Pisa, Italy
SOURCE: Fegato (1961), 7, 70-81
CODEN: FGTOAW; ISSN: 0014-9659
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Prednisone alone or in combination with 4-chlorotestosterone increased the amino-aciduria and amino-acidemia but the effect was less pronounced in case of combined administration.

IT Cirrhosis
(amino acid metabolism in, effect of 4-chlorotestosterone and prednisone on)

IT Amino acids
(metabolism of, effect of 4-chlorotestosterone and prednisone on, in cirrhosis)

IT 53-03-2, Pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-
855-19-6, Androst-4-en-3-one, 4-chloro-17β- hydroxy-, acetate
(in amino acid metabolism in cirrhosis)

L26 ANSWER 5 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:410301 CAPLUS
DOCUMENT NUMBER: 63:10301
ORIGINAL REFERENCE NO.: 63:1825f-h
TITLE: Steroids. IV. Chromatography of some androstene derivatives
AUTHOR(S): Gerali, G.; Lugaro, G.; Ferrari, L.
CORPORATE SOURCE: Univ. Milan
SOURCE: Farmaco, Edizione Scientifica (1965), 20(2), 148-57
CODEN: FRPSAX; ISSN: 0430-0920
DOCUMENT TYPE: Journal
LANGUAGE: Italian

AB cf. CA 62, 9189a. The separation of some steroids derived from androstene was studied by thin-layer chromatography on silicagel G, employing the following eluent solvent systems: (A) EtOAc 1007, C6H6 100, AcOH 40 (stirred with 20 cc. H2O and separated the aqueous phase); (B) EtOAc 40, C6H6 80, hexane 60; (C) hexane 40, EtOAc 55, MeOH 5; (D) CHCl3 90, EtOH 10; (E) C5H5N 5, hexane 55, Me2CO 50; (F) C6H6 100, hexane 100, EtOAc 50 (stirred with 20 cc. H2O as above). The values of Rf, Rs, and Rm of the following compds., with the different eluent solns., were tabulated: 5-androsten-3β-ol-17-one, 5- androsten -3β-ol-17-one 3-acetate, 5- androstene-3β,17β- diol, 5-androstene-3β,17β-diol acetate, 16-hydroxymethylene-5-androsten-3β-ol-17-one, 3β,-17-dihydroxy-5- androsteno[17,16-d]isoxazoline, 16β-cyano-5- androsten-3β-ol-17-one, 16β-cyano-5- androstene-3β,17β-diol, 16β-cyano-5- androstene-3β,17β-diol diacetate, 16-carboxy-5- androstene-3β,17β-diol, 16-carbomethoxy-5- androstene-3β, 17β-diol, 16-carbomethoxy-5- androstene-3β,17β-diol diacetate, 16β-cyano-5- androsten-3β-ol-17-one 17-oxime, 17β- amino -16βcyano-5- androsten-3β-ol, 17β- amino -16β-cyano-5- androsten-3β-ol 3,17-diacetate, 5,16-pregnadien-3β-ol-20-one 3-acetate, 16α-cyano-5-pregnen-3β-ol-20-one, 16α-cyano-5-pregnen-3β-ol-20-one 3-acetate, 16α-cyano-5-pregnen-3β-ol-20-one 3-acetate 20-oxime, 17β-amino-16α-cyano-5- androsten-3β-ol, 3,17-diacetate. By changing the eluent solution, a good, even quant. separation of these compds. could be accomplished.

IT Steroids
(chromatography of)

IT 53-43-0, Androst-5-en-17-one, 3β- hydroxy- 521-17-5, Androst-5-ene-3β,17β-diol 853-23-6, Androst-5-en-17-one, 3β- hydroxy-, acetate 979-02-2, Pregna-5,16-dien-20-one, 3β- hydroxy-, acetate 1434-54-4, Pregn-5-ene-16α-carbonitrile, 3β- hydroxy-20-oxo- 1922-26-5, Pregn-5-ene-16α-carbonitrile, 3β- hydroxy-20-oxo-, acetate 2099-12-9, Androst -5-ene-16β-carbonitrile, 3β- hydroxy-17-oxo- 2099-14-1, Androst-5-ene-16β-carbonitrile, 3β,17β-dihydroxy-, diacetate 2099-15-2, Androst -5-ene-16-carboxylic acid, 3β,17β-dihydroxy- 2099-18-5, Androst-5-ene-16β-carbonitrile, 3β- hydroxy -17-oxo-, oxime 2099-22-1, Pregn-5-ene-16α-carbonitrile, 3β-hydroxy-20-oxo-, oxime, acetate 2099-26-5, Androst -5-ene-3β,17β-diol, diacetate 2099-27-6, 6bH-Naphth[2',1':4,5]indeno[1,2-d]isoxazole-2,6b-diol, 1,2,3,4,4a,4b,5,6,6a,9,10,10a,10b,11-tetradecahydro-4a,6a-dimethyl- 2099-27-6, Androst-5-eno[17,16-d]-2'-isoxazoline-3β,17-diol

2099-44-7, Androst-5-ene-16β-carbonitrile, 3β,17β-dihydroxy- 2405-43-8, Androst-5-en-17-one, 3β- hydroxy-16-(hydroxymethylene)- 2405-45-0, Androst-5-ene-16β-carbonitrile, 17β- amino -3β- hydroxy- 2956-19-6, Androst -5-ene-16-carboxylic acid, 3β,17β-dihydroxy-, methyl ester, diacetate 3022-87-5, Androst-5-ene-16-carboxylic acid, 3β,17β-dihydroxy-, methyl ester
(chromatography of)

L26 ANSWER 6 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:423385 CAPLUS
DOCUMENT NUMBER: 57:23385
ORIGINAL REFERENCE NO.: 57:4731b-i,4732a-b
TITLE: 16-Heterocyclic amino steroids
INVENTOR(S): Hewett, Colin Leslie
PATENT ASSIGNEE(S): Organon, Inc.
SOURCE: 4 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3026318		19620320	US 1960-44861	19600725
DE 1159435			DE	
GB 933151			GB	
PRIORITY APPLN. INFO.:			GB	19590723

AB A solution of 3β,17-diacetoxy-16- androstene (50 g.) in CH_2Cl_2 (300 ml.) was cooled to -15° and Br (7.5 ml.) in CH_2Cl_2 (25 ml.) was added; immediately thereafter the solution was evaporated to dryness under reduced pressure, and the residue recrystd. to give 52 g. 3β-acetoxy-16α-bromoandrostan-17-one (I), m. 172° (Et_2O). I (15 g.) in piperidine (II) (90 ml.) was refluxed 1 hr., most of the II distilled, and diluted with H_2O. The precipitate obtained was boiled in MeOH (150 ml.) 30 min. with KOH (2 g.) in H_2O (2 ml.) to give 3β-hydroxy-16β-piperidinoandrostan-17-one (III). m. 170-5° (Me_2CO). Addition of concentrated HCl to III in MeOH and evaporation gave III.HCl, m. 265°. III (4 g.) in MeOH (25 ml.) with KBH_4 (1.5 g.) 3 hrs. gave 3β,17β-dihydroxy-16β-piperidinoandrostane, m. 185°. I (36 g.) in MeOH (1 l.) with 50% H_2SO_4 (10 ml.) was refluxed 3 hrs. to give 3β- hydroxy-16α-bromoandrostane-17-one (IV), m. 174°. IV (24 g.) in CH_2Cl_2 (150 ml.) and AcOH (200 ml.) was treated with CrO_3 (5.25 g.) in 80% AcOH (100 ml.) at room temperature 90 min. to give 22.5 g. 16α-bromoandrostane-3,17-dione (V), m. 185-7°. V (15 g.) in II (100 ml.) was refluxed 1 hr., extracted with 1% HCl, filtered hot, and the filtrate basified; Al_2O_3 chromatography of the precipitate gave 16β-piperidinoandrostane-3,17-dione (VI), m. 137°; VI. HCl m. 260-70°. KBH_4 reduction of VI 3-ketal gave 16 β-piperidino-17β-hydroxyandrostan-3-one (VII), m. 177°; VII.HCl m. 305° (decomposition). Similarly, 3β-hydroxy-16βmorpholinoandrostan-17-one (VIII), m. 192-7° (VIII.HCl m. 265°) was prepared by treating the corresponding 16-Br compound (19 g.) with morpholine (60 ml.). Reduction of VIII with $NaBH_4$ gave 3β,17β-dihydroxy-16β-morpholinoandrostane (IX), m. 265°; IX.HCl m. 320°; IX citrate m. 260°. In an analogous manner, V was converted to 16βmorpholinoandrostane-3,17-dione (X), m. 230°; X.HCl m. 225°. Reduction of X 3-ketal (17.5 g.) with KBH_4 (2 g.) gave 16β-morpholino-17β-hydroxyandrostan-3-one (XI), m.

209-10°. X (7 g.) in MeI (70 ml.) at room temperature overnight gave N-methyl-N-16β-(3,17-dioxoandrostanyl)morpholinium iodide (XII), m. 255-7° (H_2O). XII in boiling H_2O (300 ml.) was treated with AgOH and the solution filtered, concentrated to 50 ml., and kept at 0° 2 days to give N-methyl-N-16β-(3,17-dioxoandrostanyl)morpholinium hydroxide. Similarly, N-methyl-N-16β-(3-oxo- 17β-hydroxyandrostanyl)-morpholinium iodide, m. 238-40°, and the corresponding morpholinium hydroxide were prepared 3β- Hydroxy-16-bromoandrost-5-en-17-one was treated with 3 vols. morpholine to give 3β- hydroxy -16β-morpholinoandrost-5-en-17-one (XIII), m. 200°. Reduction of XIII with KBH_4 gave the corresponding 17β- hydroxy compound (XIV), m. 190°. In the same manner, 3β- hydroxy -16β-piperidinoandrost-5-en-17-one, m. 170°, and 3β,17β-dihydroxy-16β-piperidinoandrost-5-ene (XV), m. 228-30°, were prepared 16α-Bromoandrost-4-ene-3,17-dione was treated in the same manner to give 16β-morpholinoandrost-4-ene-3,17-dione (XVI), m. 198200°, and the 3,17-diol (XVII), m. 252-3°. XVII (11 g.) in PhMe (750 ml.) and cyclohexanone (110 ml.) was refluxed with aluminum isopropoxide (5.5 g.) 20 min. gave 16β-morpholinotestosterone, m. 191-3°. In a similar manner 16β-piperidinoandrost-4-ene-3,17-dione, m. 1645°, and 16β-piperidinotestosterone, m. 171-2°, were prepared Reduction of 16α-bromo-3β-hydroxyanchost-5-ene-17-one with KBH_4 gave 16α-bromo-3β,17α- dihydroxyandrost - 5 -ene (XVIII), m. 239-40°, and 16α-bromo-3β,17β-dihydroxyandrost-5-ene (XIX), m. 184-5°. XIX (0.25 g.) and II (2.5 ml.) was refluxed 3 hrs. to give XV. XVIII gave 16β-piperidino-3β,17α-dihydroxyandrost-5-ene, m. 239-40°. 3α-Acetoxyetiocholan-17-one (60 g.) in isopropenyl acetate (420 ml.) and 2% H_2SO_4 (5 ml.) was boiled 2 hrs. to give 3α,17-diacetoxy-16-etiocholene (XX) (30.8 g.), m. 90-1°. In an analogous manner, the following compds. were prepared, resp.: 16α-bromoetiocholan-17-one (XXI), m. 217-18°; 3α- hydroxy derivative of XXI, m. 212-13°; 16α-bromoetiocholane-3,17-dione, m. 194-6°; 3α-hydroxy-16β-morpholinoetiocholan-17-one (XXII), m. 234-5°; 3,17-dione derivative of XXII, m. 214-15°; 3α,17β-dihydroxy derivative of XXII, m. 210-12°; 17β-hydroxy-3-one derivative of XII, in. 229-30°; 3α-hydroxy-16β-piperidinoetiocholan-17-one (XXIII), m. 212-14°; 3,17-dione derivative of XXIII, m. 198-200°; 3α,17-dihydroxy derivative of XXIII, m. 185-6°: 17β-hydroxy-3-one derivative of XXIII, m. 185-6°; 16α-bromoestrone 3-acetate (XXIV), m. 170-1°; 16β-morpholinoestrone 3-acetate. m. 227-9°; 16β-piperidinoestradiol, m. 298° and 3β,17βdiacetoxy-16-acetamido-5-androstene, m. 271°.

IT Spectra, visible and ultraviolet
(of 15,17-dibenzylidene-3β- hydroxy-10-methyl-5α,13ξ-gonan-16-one)

IT 5α- Androstan-17-one, 3β- hydroxy -16β-morpholino-, hydrochloride
5α- Androstan-17-one, 3β- hydroxy -16β-piperidino-, hydrochloride
5α- Androstan-3-one, 17β- hydroxy -16β-morpholino-, methiodide
5α- Androstan-3-one, 17β- hydroxy -16β-morpholino-, methohydroxide
5α- Androstan-3-one, 17β- hydroxy -16β-piperidino-, hydrochloride
5α- Androstane 3β,17β-diol, 16β-morpholino-, citrate, hydrochloride
5α- Androstane 3β,17β-diol, 16β-morpholino-, hydrochloride

5α- Androstane-3,17-dione, 16β-piperidino-,
hydrochloide
5β- Androstane-3α,17-diol, 16β-piperidino-

IT 1239-35-6, Estra-1,3,5(10-trien-17-one, 16α-bromo-3- hydroxy
-, acetate 1242-55-3, 5α- Androstan-17-one,
16α-bromo-3β- hydroxy-, acetate 3000-34-8, 5α-
Androstan-17-one, 3β- hydroxy-16β-morpholino-
3136-46-7, 5α- Androstane-3,17-dione, 16β-piperidino-
5964-86-3, 5β- Androstane-3,17-dione, 16β-piperidino-
5976-46-5, 5α- Androstan-3-one, 17β- hydroxy
-16β-piperidino- 5986-82-3, 5α- Androstan-3-one,
17β- hydroxy-16β-morpholino- 5986-83-4,
Androst-5-ene-3β,17β-diol, 16β-bromo- 5986-84-5,
Androst-5-ene-3β,17α-diol, 16β-bromo- 5986-89-0,
5α- Androstane-3,17-dione, 16β-morpholino-
5986-90-3, Androst-5-en-17-one, 3β- hydroxy
-16β-piperidino- 5986-91-4, Androst-5-en-17-one, 3β-
hydroxy-16β-morpholino- 5986-92-5, Androst
-4-ene-3,17-dione, 16β-piperidino- 5986-93-6, 5β-
Androstan-17-one, 3α- hydroxy-16β-piperidino-
5986-94-7, 5β- Androstan-17-one, 3α- hydroxy
-16β-morpholino- 5986-95-8, 5β- Androstane
-3,17-dione, 16β-morpholino- 5986-96-9, Estra-1,3,5(10-trien-17-
one, 3-hydroxy-16β-piperidino- 5986-97-0,
Estra-1,3,5(10-trien-17-one, 3-hydroxy-16β-morpholino-
5987-00-8, Androst-5-ene-3β,17β-diol,
16β-morpholino- 5987-02-0, 5β- Androstane
-3α,17β-diol, 16β-morpholino- 5987-18-8, Androst
-5-ene-3β,17α-diol, 16α-bromo- 5987-20-2,
Androst-5-ene-3β,17β-diol, 16α-bromo- 5987-22-4,
Androst-5-ene-3β,17β-diol, 16β-piperidino-
5987-23-5, Androst-5-ene-3β,17α-diol,
16β-piperidino- 5987-27-9, 5α- Androstane
3β,17β-diol, 16β-piperidino- 6038-69-3,
Estra-1,3,5(10)-triene-3,17β-diol, 16β-morpholino- 6168-01-0,
5α- Androstane 3β,17β-diol, 16β-morpholino-
6263-56-5, 5α- Androstan-17-one, 3β- hydroxy
-16β-piperidino- 28507-02-0, 5α- Androstan
-17-one, 16α-bromo-3β- hydroxy- 63230-50-2, 5β-
Androst-16-ene-3α,17-diol, diacetate 94441-01-7, 5α-
Androstane-3,17-dione, 16α-bromo- 95487-08-4,
Androst-4-ene-3,17-diol, 16β-morpholino- 95557-64-5,
Androst-4-ene-3,17-dione, 16β-morpholino- 95671-35-5,
5β- Androstane-3,17-dione, 16α-bromo- 96366-05-1,
Androst-4-en-3-one, 17β- hydroxy-16β-morpholino-
96505-87-2, Androst-4-en-3-one, 17β- hydroxy
-16β-piperidino- 97155-52-7, 5α,13ξ-Gonan-16-one,
15,17-dibenzylidene-3β- hydroxy-10-methyl- 102213-27-4,
4-(17β- Hydroxy-3-oxo-5α- androstan
-16β-yl)-4-methylmorpholinium iodide 103004-99-5,
4-(3,17-Dioxo-5α- androstan-16β-yl)-4-
methylmorpholinium iodide 106951-86-4, 4-(17β- Hydroxy
-3-oxo-5α- androstan-16β-yl)-4-methylmorpholinium
hydroxide 107661-44-9, 4-(3,17-Dioxo-5α- androstan
-16β-yl)-4-methylmorpholinium hydroxide 757207-80-0, 5α-
Androstane-3,17-dione, 16α-piperidino- 877930-43-3,
5α- Androstane-3,17-dione, 16β-morpholino-,
methohydroxide 877930-44-4, 5α- Androstane-3,17-dione,
16β-morpholino-, methiodide 877930-46-6, 5α-
Androstane-3,17-dione, 16β-morpholino-, hydrochloride
877930-71-7, 5β- Androstane-3α,17β-diol,
16α-morpholino- 886200-46-0, 5β- Androstan-17-one,
16α-bromo-3α- hydroxy-, acetate 886200-48-2,

5β- Androstan-17-one, 16α-bromo-3α-
hydroxy- 886200-71-1, 5α- Androstan-3-one,
17β- hydroxy-16α-piperidino- 886200-73-3, 5β-
Androstan-3-one, 17β- hydroxy-16β-piperidino-
886200-75-5, 5β- Androstan-3-one, 17β- hydroxy
-16β-morpholino- 888713-28-8, Estra-1,3,5(10)-triene-3,17-diol,
16β-piperidino-
(preparation of)

L26 ANSWER 7 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:590003 CAPLUS
DOCUMENT NUMBER: 111:190003
TITLE: Human placental 3β- hydroxy
-5-ene-steroid dehydrogenase and steroid 5 →
4-ene isomerase: purification from mitochondria and
kinetic profiles, biophysical characterization of the
purified mitochondrial and microsomal enzymes
AUTHOR(S): Thomas, James L.; Myers, Richard P.; Strickler, Ronald
C.
CORPORATE SOURCE: Sch. Med., Washington Univ., St Louis, MO, 63110, USA
SOURCE: Journal of Steroid Biochemistry (1989), 33(2), 209-17
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In human placenta, 3β- hydroxy-Δ5-steroid
dehydrogenase (EC 1.1.1.145) and steroid Δ-isomerase (EC 5.3.3.1),
an enzyme complex found in microsomes and mitochondria, synthesizes
progesterone from pregnenolone and androstenedione from fetal
dehydroepiandrosterone sulfate. The dehydrogenase and isomerase
activities of the mitochondrial enzyme were copurified (733-fold) using
sequential cholate solubilization, ion-exchange chromatog. (DEAE-Toyopearl
650S), and hydroxylapatite chromatog. (Bio-Gel HT). Enzyme homogeneity
was demonstrated by a single protein band in SDS-PAGE (monomeric mol. weight
= 41,000), gel filtration at constant specific enzyme activity (mol. weight =
77,000), and a single N-terminal sequence. Kinetic constant specific enzyme
activity (mol. weight = 77,000), and a single N-terminal sequence. Kinetic
constant were determine for the oxidation of pregnenolone (Km = 1.6 μM, Vmax =
48.6 nmol/min/mg) and dehydroepiandrosterone (Km = 2.4 μM, Vmax = 48.5
nmol/min/mg) and for the isomerization of 5-pregnene-3,20-dione (Km = 9.3
μM, Vmax = 914.2 nmol/min/mg) and 5- androstene-3,17-dione (Km
= 27.6 μM, Vmax = 888.4 nmol/min/mg. Mixed substrate studies showed
that the dehydrogenase and isomerase activities utilize their resp.
pregnene and androstene substrates competitively. Dixon anal.
demonstrated that the product steroids, progesterone and
androstenedione, were competitive inhibitors of the C-21 and C-19
dehydrogenase activities. Enzyme purified from mitochondria and
microsomes had similar kinetic profiles with respect to substrate
utilization, product inhibition, and cofactor (NAD) reduction (mean Km using
C-19 and C-21 dehydrogenase substrates = 26.4 μM; mean Vmax = 73.2
nmol/min/mg). Pure enzyme from both organelles exhibited identical
biophys. properties in terms of mol. weight and subunit composition, pH optima
(pH
9.8, dehydrogenase; pH 7.5, isomerase), temperature optimum (37°), stability in
storage and solution, effects of divalent cations, and the single N-terminal
sequence of 27 amino acids. The results suggested that the
mitochondrial and microsomal enzymes are the same protein localized in
different organelles.
IT Placenta
(hydroxy steroid dehydrogenase-steroid isomerase complex of
microsomes and mitochondria of, of human)
IT Microsome
Mitochondria
(hydroxy steroid dehydrogenase-steroid isomerase complex of,

of human placenta)
IT Protein sequences
(of hydroxy steroid dehydrogenase-steroid isomerase complex N-terminal region, of human placenta microsomes and mitochondria)
IT Michaelis constant
(of hydroxy steroid dehydrogenase-steroid isomerase complex, of human placenta microsomes and mitochondria)
IT Kinetics, enzymic
(of inhibition, of hydroxy steroid dehydrogenase of human placenta mitochondria, by androstenedione and progesterone)
IT Cations
(divalent, hydroxy steroid dehydrogenase and steroid isomerase of human placenta response to)
IT 57-83-0, Progesterone, biological studies 63-05-8, 4-Androstene-3,17-dione
RL: BIOL (Biological study)
(hydroxy steroid dehydrogenase of human placenta inhibition by, kinetics of)
IT 9031-36-1DP, hydroxy steroid dehydrogenase complexes 9044-85-3DP, steroid isomerase complexes
RL: PREP (Preparation)
(of placenta microsomes and mitochondria, of human, purification and characterization of)
IT 53-43-0, Dehydroepiandrosterone 53-84-9, NAD 145-13-1 571-36-8, 5-Androstene-3,17-dione
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with hydroxy steroid dehydrogenase-steroid isomerase complex of human placenta, kinetics of)

L26 ANSWER 8 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:173614 CAPLUS
DOCUMENT NUMBER: 143:387223
TITLE: Solid-phase synthesis of model libraries of 3α,17β-dihydroxy-16α-(N-substituted-aminoethyl)-5α- androstanes for the development of steroidal therapeutic agents
AUTHOR(S): Maltais, Rene; Mercier, Caroline; Labrie, Fernand; Poirier, Donald
CORPORATE SOURCE: Oncology and Molecular Endocrinology Research Center (Medicinal Chemistry Division), University Laval, Centre Hospitalier Universitaire de Quebec (CHUQ), QC, G1V 4G2, Can.
SOURCE: Molecular Diversity (2005), 9(1-3), 67-79
CODEN: MODIF4; ISSN: 1381-1991
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:387223
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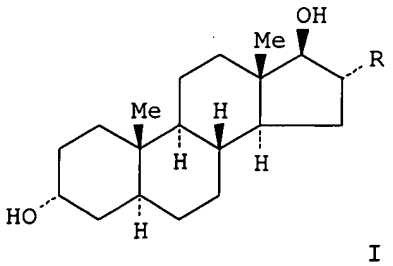


I

AB The solid-phase synthesis of 16α-derivs. e.g., I [R = CH2CH2NHR1COR3, CH2CH2NHR1R2COR3; R1 = Gly, L-Pro, L-Ile, L-Phe, bond; R2 = Gly, L-Pro, L-Ile, L-Phe; R3 = CH2Et, (CH2)4Br, (CH2)4Me, cyclohexyl, Ph, CH2Ph, CH2C6H4(OCH2CH2-piperidin-1-yl)-4], of 5α-androstane-3α,17β-diol with one, two or three levels of mol. diversity was accomplished using the diethylsilyloxy linker. Libraries with one level of diversity (10 members) and two levels of diversity (40 members) were synthesized in a parallel fashion in good yields and acceptable HPLC purities for the majority of library members. Compds. with three levels of diversity (15 pools) were realized in a split and pool fashion to allow further deconvolution by the positional scanning method. The screening of the generated model libraries revealed interesting preliminary structure-activity relationships related to their antiproliferative activities on androgen-sensitive Shionogi cells. In the case of the two-level library, the presence of a hydrophobic amino acid at R1 (isoleucine (Ile) or phenylalanine (Phe)) and a six-membered ring (aromatic or not) at R2 seems an important requirement for activity. In the three-level library, the amino acid residues isoleucine and phenylalanine clearly provided a better antiproliferative activity than glycine (Gly) and proline (Pro). These model libraries will serve as basis for the generation of larger libraries of peptidosteroids toward the development of therapeutic agents.

IT Amino acids, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation by, of 16α-(aminoethyl)-5α- androstane -3α,17β-diols; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT Carboxylic acids, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation by, of amino acid 16α-(aminoethyl)-5α- androstane amides; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT Steroids, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(androstanediols, aminoethylated; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α-androstane-3α,17β-diols)

IT Structure-activity relationship
(antiproliferative; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT Cell proliferation
(inductors; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT Peptides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptidosteroids, as therapeutic agents; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α-androstane-3α,17β-diols)

IT Antiandrogens
Chemical library
Cytotoxic agents
Solid phase synthesis
(solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 79-09-4, Propionic acid, reactions
RL: CRT (Combinatorial reactant); RCT (Reactant); CMBI (Combinatorial study); RACT (Reactant or reagent)
(acylation by, of amino acid 16α-(2-aminoethyl)-5α- androstane amide; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α-androstane-3α,17β-diols)

IT 65-85-0, Benzoic acid, reactions 98-89-5, Cyclohexanecarboxylic acid 103-82-2, Phenylacetic acid, reactions 107-92-6, Butanoic acid, reactions 142-62-1, Hexanoic acid, reactions 2067-33-6, 5-Bromopentanoic acid 3235-67-4, Piperidinoacetic acid 28356-58-3, 4-Pyridineacetic acid 89407-98-7, 4-(2-Piperidinoethoxy)benzoic acid 295319-66-3, [4-(2-Piperidinoethoxy)phenyl]acetic acid
RL: CRT (Combinatorial reactant); RCT (Reactant); CMBI (Combinatorial study); RACT (Reactant or reagent)
(acylation by, of amino acid 16α-(aminoethyl)-5α-androstane amide; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 29022-11-5, Fmoc-glycine 35661-40-6, Fmoc-L-phenylalanine 71989-23-6 71989-31-6, Fmoc-L-proline
RL: CRT (Combinatorial reactant); RCT (Reactant); CMBI (Combinatorial study); RACT (Reactant or reagent)
(acylation by, of resin-bound (aminoethyl)androstanediol THP ether; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 96-32-2, Methyl bromoacetate
RL: CRT (Combinatorial reactant); RCT (Reactant); CMBI (Combinatorial study); RACT (Reactant or reagent)
(alkylation by, of hydroxyandrostanone; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α-androstane-3α,17β-diols)

IT 1852-53-5, 5α- Androstane-3α,17β-diol 479063-41-7, 16α-(3-Bromopropyl)-5α- androstane -3α,17β-diol 866612-89-7, 16α-(2-Aminoethyl)-5α-androstane-3α,17β-diol
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative activity of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 866591-92-6DP, 3-O-PS-DES resin-bound 866591-93-7DP, 3-O-PS-DES resin-bound 866591-94-8DP, 3-O-PS-DES resin-bound 866591-95-9DP, 3-O-PS-DES resin-bound 886996-53-8DP, 3-O-PS-DES resin-bound
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-acylation of, with carboxylic acids; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 866591-88-0DP, 3-O-PS-DES resin-bound 866591-90-4DP, 3-O-PS-DES resin-bound 866591-91-5DP, 3-O-PS-DES resin-bound
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-deprotection of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 866591-89-1DP, 3-O-PS-DES resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and N-deprotection of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 866591-36-8DP, 3-O-PS-DES resin-bound
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acylation of, with amino or carboxylic acids; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 57711-45-2P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and alkylation of, by bromoacetate; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 866591-38-0P 866591-39-1P 866591-40-4P 866591-41-5P 866591-42-6P
866591-43-7P 866591-44-8P 866591-45-9P 866591-46-0P 866591-47-1P
866591-48-2P 866591-49-3P 866591-50-6P 866591-51-7P 866591-52-8P
866591-53-9P 866591-54-0P 866591-55-1P 866591-56-2P 866591-57-3P
866591-58-4P 866591-59-5P 866591-60-8P 866591-61-9P 866591-62-0P
866591-63-1P 866591-64-2P 866591-65-3P 866591-66-4P 866591-67-5P
866591-68-6P 866591-69-7P 866591-70-0P 866591-71-1P 866591-72-2P
866591-73-3P 866591-74-4P 866591-75-5P 866591-76-6P 866591-77-7P
866591-78-8P 866591-79-9P 866591-80-2P 866591-81-3P 866591-82-4P
866591-83-5P 866591-84-6P 866591-85-7P 866591-86-8P 866591-87-9P
866592-46-3P 866592-47-4P 866592-48-5P 866592-49-6P 866592-50-9P
866592-51-0P 866592-52-1P 866592-53-2P 866592-54-3P 866592-55-4P
866592-56-5P 866592-57-6P 866592-58-7P 866592-59-8P 866592-60-1P
866592-61-2P 866592-62-3P 866592-63-4P 866592-64-5P 866592-65-6P
866592-66-7P 866592-67-8P 866592-68-9P 866592-69-0P 866592-70-3P
866592-71-4P 866592-72-5P 866592-73-6P
RL: CPN (Combinatorial preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(preparation and antiproliferative activity of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 866591-32-4P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and azidation of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 866591-35-7DP, 3-O-PS-DES resin-bound
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and azide reduction of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 866591-34-6P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and binding of, to PS-DES resin; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 866591-33-5P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and desilylation of; solid-phase synthesis of chemical library of
16α-(N-substituted-aminoethyl)-5α- androstane
-3α,17β-diols)
IT 866591-30-2P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and regioselective bromination of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α-
androstane-3α,17β-diols)
IT 866591-96-0DP, 3-O-PS-DES resin-bound 866591-97-1DP, 3-O-PS-DES resin-bound 866591-98-2DP, 3-O-PS-DES resin-bound 866591-99-3DP, 3-O-PS-DES resin-bound 866592-00-9DP, 3-O-PS-DES resin-bound 866592-01-0DP, 3-O-PS-DES resin-bound 866592-02-1DP, 3-O-PS-DES resin-bound 866592-03-2DP, 3-O-PS-DES resin-bound 866592-04-3DP, 3-O-PS-DES resin-bound 866592-05-4DP, 3-O-PS-DES resin-bound 866592-06-5DP, 3-O-PS-DES resin-bound 866592-07-6DP, 3-O-PS-DES resin-bound 866592-08-7DP, 3-O-PS-DES resin-bound 866592-09-8DP, 3-O-PS-DES resin-bound 866592-10-1DP, 3-O-PS-DES resin-bound 866592-11-2DP, 3-O-PS-DES resin-bound 866592-12-3DP, 3-O-PS-DES resin-bound 866592-13-4DP, 3-O-PS-DES resin-bound 866592-14-5DP, 3-O-PS-DES resin-bound 866592-15-6DP, 3-O-PS-DES resin-bound 866592-16-7DP, 3-O-PS-DES resin-bound 866592-17-8DP, 3-O-PS-DES resin-bound 866592-18-9DP, 3-O-PS-DES resin-bound 866592-19-0DP, 3-O-PS-DES resin-bound 866592-20-3DP, 3-O-PS-DES resin-bound 866592-21-4DP, 3-O-PS-DES resin-bound 866592-22-5DP, 3-O-PS-DES resin-bound 866592-23-6DP, 3-O-PS-DES resin-bound 866592-24-7DP, 3-O-PS-DES resin-bound 866592-25-8DP, 3-O-PS-DES resin-bound 866592-26-9DP, 3-O-PS-DES resin-bound 866592-27-0DP, 3-O-PS-DES resin-bound 866592-28-1DP, 3-O-PS-DES resin-bound 866592-29-2DP, 3-O-PS-DES resin-bound 866592-30-5DP, 3-O-PS-DES resin-bound 866592-31-6DP, 3-O-PS-DES resin-bound 866592-32-7DP, 3-O-PS-DES resin-bound 866592-33-8DP, 3-O-PS-DES resin-bound 866592-34-9DP, 3-O-PS-DES resin-bound 866592-35-0DP, 3-O-PS-DES resin-bound 866592-36-1DP, 3-O-PS-DES resin-bound 866592-37-2DP, 3-O-PS-DES resin-bound 866592-38-3DP, 3-O-PS-DES resin-bound 866592-39-4DP, 3-O-PS-DES resin-bound 866592-40-7DP, 3-O-PS-DES resin-bound 866592-41-8DP, 3-O-PS-DES resin-bound 866592-42-9DP, 3-O-PS-DES resin-bound 866592-43-0DP, 3-O-PS-DES resin-bound 866592-44-1DP, 3-O-PS-DES resin-bound 866592-45-2DP, 3-O-PS-DES resin-bound
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and removal of, from resin; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α-
androstane-3α,17β-diols)
IT 866591-29-9P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and stereoselective reduction of; solid-phase synthesis of chemical
library of 16α-(N-substituted-aminoethyl)-5α-
androstane-3α,17β-diols)
IT 866591-31-3P
RL: CPN (Combinatorial preparation); CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)

(preparation and tetrahydropyranylation of; solid-phase synthesis of chemical
library of 16α-(N-substituted-aminoethyl)-5α-androstane-3α,17β-diols)

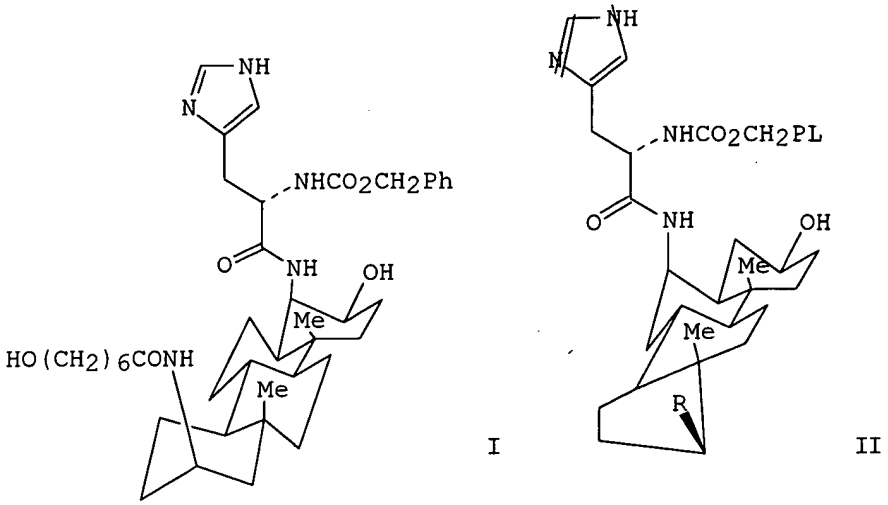
IT 53-41-8, 3α- Hydroxy-5α- androstan-17-one
RL: CRT (Combinatorial reactant); RCT (Reactant); CMBI (Combinatorial study); RACT (Reactant or reagent)
(silylation of; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

IT 866591-37-9P 866592-74-7P 866592-75-8P 866592-76-9P 866592-77-0P
866592-78-1P 866592-79-2P 866592-80-5P 866592-81-6P 866592-82-7P
866592-83-8P 866592-84-9P 866592-85-0P 866592-86-1P 866592-87-2P
866592-88-3P 866592-89-4P 866592-90-7P 866592-91-8P 866592-92-9P
866592-93-0P 866592-94-1P 866592-95-2P 866592-96-3P 866592-97-4P
866592-98-5P 866592-99-6P 866593-00-2P 866593-01-3P 866593-02-4P
866593-03-5P 866593-04-6P 866593-05-7P 866593-06-8P 866593-07-9P
866593-08-0P 866593-09-1P 866593-10-4P 866593-11-5P 866593-12-6P
866593-13-7P 866593-14-8P 866593-15-9P 866593-17-1P 866593-19-3P
866593-21-7P 866593-23-9P 866593-24-0P 866593-25-1P 866593-26-2P
866593-27-3P 866593-28-4P 866593-29-5P 866593-30-8P 866593-31-9P
866593-32-0P 866593-33-1P 866593-34-2P 866593-35-3P 866593-36-4P
866593-37-5P 866593-38-6P 866593-39-7P 866593-40-0P 866593-41-1P
866593-42-2P 866593-43-3P 866593-44-4P 866593-45-5P 866593-46-6P
866593-47-7P 866593-48-8P 866593-49-9P 866593-50-2P 866593-51-3P
866593-52-4P 866593-53-5P 866593-54-6P 866593-55-7P 866593-56-8P
866593-57-9P 866593-58-0P 866593-59-1P 866593-60-4P 866593-61-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane-3α,17β-diols)

IT 9003-53-6D, Polystyrene, chlorodiethylsilylated (DES) resin
RL: CUS (Combinatorial use); NUU (Other use, unclassified); CMBI (Combinatorial study); USES (Uses)
(support for solid synthesis; solid-phase synthesis of chemical library of 16α-(N-substituted-aminoethyl)-5α- androstane -3α,17β-diols)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 9 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1978:38055 CAPLUS
DOCUMENT NUMBER: 88:38055
TITLE: Bifunctional catalysts. IV. Synthesis and catalytic action of steroids with an alcohol function and imidazole nucleus
AUTHOR(S): Fetizon, M.; Jaudon, P.
CORPORATE SOURCE: Lab. Synth. Org., Ec. Polytech., Palaiseau, Fr.
SOURCE: Tetrahedron (1977), 33(13), 1619-24
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: French
GI



AB The diamino steroids I and II [R = NHCO(CH2)6OH] were prepared from 17β- amino-17aα-methyl-3β-D-homoandrost-5-ene and 17β- amino-3β-hydroxyandrost-5-ene, resp., by sequential condensation with a heptanoic acid derivative, nitration, reduction, condensation and N-benzyloxycarbonylhistidine, and saponification The catalytic effect of I and II [R = NHCO(CH2)6OH, H) on the hydrolysis of AcOC6H4NO2-4 was studied. A slight acceleration was observed with compds. in which hydroxy and imidazole groups are attached to the steroid skeleton. The acceleration was greater with I than with II [R = NHCO(CH2)6OH].

IT Hydrolysis catalysts
(bifunctional steroids, for nitrophenyl acetate)

IT Kinetics of hydrolysis
(of nitrophenyl acetate, steroid-catalyzed)

IT Steroids, uses and miscellaneous
D-Homosteroids
(bifunctional, catalysts, for hydrolysis of nitrophenyl acetate)

IT 65351-84-0
RL: CAT (Catalyst use); USES (Uses)
(catalyst, for hydrolysis of nitrophenyl acetate)

IT 65351-85-1 65351-86-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with histidine derivative)

IT 14997-58-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation reaction of, with aminoandrostene and aminohomoandrostene derivs.)

IT 4350-66-7 65351-74-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation reaction of, with hydroxyheptanoic acid derivs.)

IT 830-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrolysis of, steroid-catalyzed, kinetics of)

IT 502-42-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidation of)

IT 3710-42-7P 65351-69-1P 65351-70-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and condensation reactions of, with aminohydroxyandrostene and aminomethylhydroxyhomoandrostene)

IT 65351-71-5P 65351-72-6P 65351-73-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

IT 65351-75-9P 65351-76-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and nitration of)

IT 65351-79-3P 65351-80-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)

IT 65351-81-7P 65374-37-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)

IT 65351-77-1P 65351-78-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT 65351-82-8P 65351-83-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as catalyst, for hydrolysis of nitrophenyl acetate)

IT 6149-48-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, hydrazination , and hydrolysis of)

L26 ANSWER 10 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1964:440612 CAPLUS
DOCUMENT NUMBER: 61:40612
ORIGINAL REFERENCE NO.: 61:7075c-e
TITLE: Primary amines
INVENTOR(S): De Ruggieri, Pietro; Gandolfi, Carmelo; Chiaramonti, Domenico
PATENT ASSIGNEE(S): Ormonoterapia Richter Societa per Azioni
SOURCE: 2 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3137710		19640616	US 1961-123438	19610712
DE 1173484			DE	
GB 960939			GB	
PRIORITY APPLN. INFO.:			IT	19610330

OTHER SOURCE(S): CASREACT 61:40612

AB Primary amines were prepared by the reduction of alkoxyethylideneamino compds., RN:C(OR')Me (R = aliphatic, alicyclic, or araliphatic radical and R' = M or Et), by Na-Hg or Zn-Hg in an acid medium. This methode is effective for compds. such as 16α- or 16β-methyl-17-(alkoxyethylideneamino)androstanes which are subject to strong steric hindrance. Thus, methylamine was prepared by the reaction of 1 part (1-ethoxyethylideneamino)methane, b. 99-100°, in 15 parts 3N HCl with 16 parts Na-Hg for 3 hrs. at 5-10°. The mixture was decanted from the Hg and evaporated to dryness in vacuo to give MeNH2.HCl, m. 226° (alc.-ether). Other amines prepared similarly: ethylamine, b. 16.5°; 1-amino-2-methylpropane, b. 67-9°; 1-aminopentadecane, b2 130-2°; aminocyclohexane, b7 61-3°; 17β-aminoandrost-5-en-3β-ol, b. 166-8°; 3β-acetoxy-17β-aminoandrost-5-ene, m. 133-4° (MeOH); 17β- amino-5α- androstan-3β-ol, m. 160-2° (EtOAc); 3β-acetoxy-17β- amino-5α-androstane, m. 102-5° (MeOH); 16α-methyl-17β-amino-5α- androstan-3β-ol, m. 161-3°

(MeOH); 3β-acetoxy-16α-methyl-17β- amino -5α- androstane, m. 135-7° (MeOH); 16α-methyl-17β-aminoandrost-5-en-3β-ol, m. 168-71° (MeOH); 16β-methyl-17β-aminoandrost-5-en-3β-ol, m. 194-6° (MeOH); benzylamine, b. 185°.

IT Steroids
(amino, imidic acids in manufacture of)

IT Imidic acids
(esters, primary amine manufacture from)

IT Amines
(manufacture of primary, esters of organic imidic acids in)

IT 108-91-8, Cyclohexylamine
(manufacture)

IT 74-89-5, Methylamine 75-04-7, Ethylamine 78-81-9, Isobutylamine 100-46-9, Benzylamine
(manufacture of)

IT 557-66-4, Ethylamine, hydrochloride 1039-20-9, Androst -5-en-3β-ol, 17β- amino-16α-methyl- 1039-21-0, Androst-5-en-3β-ol, 17β- amino-16β-methyl- 1048-91-5, 5α- Androstan-3β-ol, 17β- amino -16α-methyl-, acetate (ester) 2570-26-5, Pentadecylamine 4350-66-7, Androst-5-en-3β-ol, 17β- amino- 5833-82-9, Estr-5-en-17-one, 3β- hydroxy -10-vinyl- 95001-60-8, Estr-5-ene-3β,17β-diol, 17-methyl-10-vinyl-
(preparation of)

L26 ANSWER 11 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1966:458478 CAPLUS
DOCUMENT NUMBER: 65:58478
ORIGINAL REFERENCE NO.: 65:10940g-h
TITLE: An accelerated single-column procedure for the automatic analysis of amino acids in collagen and elastin hydrolyzates
AUTHOR(S): Miller, E. J.; Piez, K. A.
CORPORATE SOURCE: Natl. Insts. of Health, Bethesda, MD
SOURCE: Analytical Biochemistry (1966), 16(2), 320-6
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An accelerated single-column procedure for the automatic analysis of the amino acids in the complex hydrolyzates of collagen and elastin is presented. In addition, a modification of the starting buffer is described which eliminates the baseline drift associated with the changing composition of the column effluent. The procedure allows 3 complete amino acid analyses of collagen or elastin hydrolyzates in a working day.

IT Amino acids
(analysis of, automatic)

IT Collagen
Elastin
(analysis of, for amino acids)

IT Amino acids
(of collagen and elastin, analysis of, automatic)

IT 53-43-0, Androst-5-en-17-one, 3β- hydroxy- 58-22-0, Testosterone 63-05-8, Androst -4-ene-3,17-dione 72-23-1, Pregn-4-ene-3,11,20-trione, 21-hydroxy- 382-44-5, Androst-4-ene-3,17-dione, 11β-hydroxy- 382-45-6, Androst-4-ene-3,11,17-trione 481-21-0, 5α-Cholestane 898-84-0, Androsta -1,4-diene-3,17-dione, 11β- hydroxy- 2681-55-2, Androst-4-ene-17β-carboxylic acid, 3-oxo-, methyl ester 3941-62-6, Androst-4-ene-17β-carboxylic acid, 17-hydroxy-3,11-dioxo-, methyl ester 5062-52-2, Androst

-4-ene-17β-carboxylic acid, 3,11-dioxo-, methyl ester 10486-85-8, Androst-4-ene-17β-carboxylic acid, 11β- hydroxy -3-oxo-, methyl ester 10486-86-9, Androst-4-ene-17β-carboxylic acid, 17-hydroxy-3-oxo-, methyl ester 10486-88-1, Androst-4-ene-17β-carboxylic acid, 11β,17-dihydroxy-3-oxo-, methyl ester 10486-89-2, Androsta-1,4-diene-17β-carboxylic acid, 11β,17-dihydroxy-3-oxo-, methyl ester
(chromatography of)

L26 ANSWER 12 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1959:67855 CAPLUS
DOCUMENT NUMBER: 53:67855
ORIGINAL REFERENCE NO.: 53:12345b-i,12346a-h
TITLE: Steroids and Walden inversion. XLI. Deamination of some A-nor-, B-nor-, and 17-aminosteroids
AUTHOR(S): Shoppee, C. W.; Sly, J. C. P.
CORPORATE SOURCE: Univ. Coll., Swansea, S. E. Wales
SOURCE: Journal of the Chemical Society (1959) 345-56
CODEN: JCSOA9; ISSN: 0368-1769
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 53:67855

AB cf. C.A. 53, 1412g. NH2 groups attached to flexible 5-membered carbocyclic systems, e.g., cyclopentane, cis-perhydroindan, appear to possess mixed equatorial-axial character. NH2 groups attached to rigid 5-membered carbocyclic systems, e.g. trans-perhydroindan, or to such systems forming part of the nuclei of A-nor-5α-, A-nor-5β- and 14α-steroids, at positions adjacent to a bridgehead, appear to possess either equatorial character disclosed by deamination with retention of configuration, or axial character disclosed by deamination with ready and exclusive elimination (Saytzew orientation); nor steroids with NH2 groups not adjacent to a bridgehead, like aliphatic amino groups, undergo deamination with predominant inversion of configuration accompanied by some elimination. Cholestanol (11 g.) oxidized 2.5 hrs. at 70-5° with 11.5 g. CrO3 in 90% AcOH gave 8.5 g. 2,3-seco-5α-cholestane-2,3-dioic acid, m. 196-7° (Et2O-pentane), which when refluxed with Ac2O and distilled at 300°/1.5 mm. gave 4.6 g. A-nor-5α-cholestan-2-one (I), m. 100-1° (MeOH); oxime m. 201-3° (EtOAc). I by reduction with excess Na in alc., or with (iso-PrO)3Al in slowly distilling (7 hrs.) PrOH gave a mixture of epimeric alcs., which were separated by overnight treatment with 4% alc. solution of digitonin. The insol. digitonide on decomposition with C5H5N gave A-nor-5α-cholestan-2α-ol (II), m. 128°, [α]D 38° (c 1.2, all rotations determined in CHCl3); acetate, m. 80°, [α]D 1° (c 0.8). The material not precipitated by digitonin gave A-nor-5α-cholestan-2β-ol (III), as solvate, m. 120° with transition to needles m. 135°, and after sublimation at 160°/0.5 mm., m. 153°, [α]D 28° (c 1.0); acetate m. 93°, [α]D 25° (c 0.4). I oxime (0.6 g.) refluxed 2 hrs. in 200 cc. AmOH saturated with Na, left 1.5 hrs., and excess Na destroyed with alc. gave 580 mg. of oil which was chromatographed on Al2O3 to give 430 mg. 2β- amino -A-nor-5α-cholestane (IV), b0.01 150°, [α]D 25.5° (c 0.9); acetyl derivative m. 190-1° (Me2CO), [α]D 39° (c 1.0). I oxime (0.5 g.) hydrogenated 6 hrs. with 200 mg. PtO2 in 50 cc. AcOH, the product acetylated, and chromatographed on Al2O3 gave 410 mg. IV N-Ac derivative 3,4-Seco-5-cholestene-3,4-dioic acid (m. 296°) was converted by refluxing with Ac2O and pyrolyzing at 300-20°/ 1.5 mm. into A-nor-5β-cholesten-3-one (V), m. 95°. Hydrogenation of V with PdO in Et2O-AcOH gave A-nor-5β-cholestan-3-one (VI), m. 74°; oxime m. 129-30°, [α]D 74° (c 0.9). VI (250 mg.) in refluxing

alc. treated 2 hrs. with Na, isolated, and chromatographed on Al_2O_3 gave 200 mg. A-nor-5β-cholestan-3β-ol (VII), m. 89° and 107°, $[\alpha]D$ 51° (c 0.9). VI (85 mg.) refluxed 1 hr. with 50 mg. $LiAlH_4$ in Et_2O gave 85 mg. of an oil which when chromatographed gave 69 mg. VII. VI (100 mg.) resisted hydrogenation in the presence of 44 mg. PtO_2 in Et_2O-AcOH containing 2 drops 60% $HClO_4$ and was recovered unchanged (97 mg.). V oxime (0.6 g.) refluxed 3 hrs. in 120 cc. AmOH saturated with Na, left 1 hr., excess Na destroyed, and the mixture poured into H_2O, extracted with Et_2O, and worked up through the Et_2O-insol. HCl salt gave 400 mg. 3β- amino-A-nor-5β-cholestane (VIII), b0.5 181-5°, $[\alpha]D$ 46° (c 0.8); Ac derivative m. 246-7°, $[\alpha]D$ 48° (c 0.9). V oxime (250 mg.) reduced 0.75 hr. in 35 cc. AcOH with 100 mg. PtO_2 and H gave 220 mg. of an oil which when chromatographed on Al_2O_3 gave 3α- amino-A-nor-5β-cholestane (IX), m. 66-8° (MeOH), $[\alpha]D$ 9° (c 1.1); Ac derivative m. 166-8°, $[\alpha]D$ 67° (c 0.9). 3β-Hydroxy-6,7-seco-5α-cholestane-6,7-dioic acid, m. 239°, was oxidized with CrO_3 in AcOH to the 3-oxo acid, m. 254-5°. The 3-oxo acid (8.3 g.) refluxed 1 hr. with 215 cc. $(CH_2OH)_2$ containing 7 cc. $N_2H_4.H_2O$ with 8.3 g. Na, the temperature allowed to rise to 185° and refluxing continued 6 hrs. gave 7.3 g. 6,7-seco-5α-cholestane-6,7-dioic acid (X), m. 272-3° (AcOH). The Ba salt of X by pyrolysis 3 hrs. at 400-20°/1.5 mm. gave B-nor-5β,8α-cholestan-6-one (XI), m. 92-3° (aqueous Me_2CO); oxime m. 185-7° (MeOH). XI (200 mg.) refluxed 1.5 hrs. in 80 cc. AmOH with Na and the crude product chromatographed gave 144 mg. B-nor-5β,8α-cholestan-6α-ol (XII), m. 85-7° (aqueous Me_2CO), $[\alpha]D$ 42° (c 1.0). XI (300 mg.) refluxed 14 hrs. with excess $LiAlH_4$ and the 290 mg. of crude product chromatographed on Al_2O_3 gave 145 mg. unchanged XI and 120 mg. XII. XII left overnight with $SOCl_2$ in C_5H_5N gave B-nor-8α-cholest-5-ene, an oil. XI oxime (215 mg.) refluxed 4 hrs. with Na and AmOH gave after chromatography 6α-amino-B-nor-5β,8α-cholestane (XIII), b1 220-30°, $[\alpha]D$ 33° (c 1.1); Ac derivative, b0.4 180-90°, m. 178-80° (Me_2CO), $[\alpha]D$ 14° (c 1.1). XI oxime (110 mg.) in 30 cc. dioxane refluxed 16 hrs. with excess $LiAlH_4$ and the crude product acetylated and chromatographed gave XIII Ac derivative XI oxime (120 mg. resisted hydrogenation in 30 cc. AcOH with 50 mg. PtO_2 at 20° and at 55-60° with 4 drops 60% $HClO_4$. 5α- Androstan-17-one oxime (XIV) (1 g.) similarly treated with Na in alc. gave 17β- amino-5α- androstane (XV), m. 138-41° (Me_2CO); Ac derivative m. 208-9° (EtOAc). XIV (0.5 g.) in 100 cc. Et_2O refluxed 3 hrs. with 1 g. $LiAlH_4$ gave 480 mg. XV. XIV (0.4 g.) hydrogenated 1 hr. with 50 cc. AcOH, 100 mg. PtO_2, and 2 drops 60% $HClO_4$ gave 380 mg. XV. 3β-Acetoxy-5- androsten-17-one oxime (XVI) (1.5 g.) similarly reduced with 100 cc. alc. and Na gave 1.3 g. 17β- amino-5-androsten-3β-ol (XVII), m. 160° (EtOAc), $[\alpha]D$ -80° (c 1.0); N,O-di-Ac derivative m. 196°, $[\alpha]D$ -88° (c 0.5). XVI (0.5 g.) in 50 cc. Et_2O refluxed 3 hrs. with excess $LiAlH_4$ gave 450 mg. XVII. 3β-Acetoxy-5-etienic acid (0.5 g.) in 20 cc. C_6H_6 refluxed 2 hrs. with 1 cc. purified $SOCl_2$, the chloride in 60 cc. 2:1 Me_2CO-dioxane treated 0.5 hr. with 300 mg. NaN_3 in 1.2 cc. H_2O, and this material heated 1.5 hrs. in C_6H_6 gave the 17β-isocyanate, which was refluxed 2 hrs. with 20 cc. AcOH and 7 cc. concentrated HCl, evaporated, and the product refluxed 1 hr. with 15% MeOHNaOH, and the base isolated through the Et_2O-insol. HCl salt and chromatographed to give 175 mg. XVII. In the following 6 expts. the steroid amine was dissolved in 50% AcOH and where necessary dioxane added to give full solution $NaNO_2$ (2-3 times the weight of amine) in 50% AcOH was added dropwise at 20°, the mixture left overnight, after basification with 4N NaOH, and the product isolated by extraction with Et_2O,

and then hydrolysis 0.5 hr. with 5% MeOH-KOH, or acetylation at 100°. (1) IV (205 mg.) gave a product which by chromatography on Al2O3 gave 5 mg. of an oil which did not crystallize, but gave a pos. test for unsatn. with C(NO2)4 in CHCl3, and is probably A-nor-5α-cholest-1(and/or -2)-ene, 125 mg. of II, and 60 mg. of an oil which by acetylation gave IV Ac derivative (2) VIII (0.6 g.) gave a product from which most of the basic material was separated by treatment with dry HCl in Et2O. The Et2O-insol. HCl salt (290 mg.) gave on acetylation VIII Ac derivative The 315 mg. of residue by chromatography gave: (a) 177 mg. A-norcholest-3(5)-ene (XVIII), m. 80°, [α]D 53° (c 1.1); (b) 119 mg. VII; and (c) 14 mg. of oil, which on acetylation gave VII Ac derivative (3) IX (210 mg.) gave 195 mg. of crude product which on chromatography gave (a) 82 mg. XVIII, and (b) 105 mg. oils which on acetylation gave IX Ac derivative (4) XIII (300 mg.) gave 280 mg. crude product which on chromatography gave (a) 50 mg. B-nor-8α-cholest-5-ene, noncryst. but gave a pos. C(NO2)4 test; (b) 146 mg. of a substance, C26H46ON2, m. 121° and 136-8°, and (c) 75 mg. of oil which on acetylation gave XIII Ac derivative (5) XV (130 mg.) gave 125 mg. 5α- androstan -17β-ol, m. 168-70° (hexane). (6) XVII (0.5 g.) gave 485 mg. androst-5-ene-3β,17β-diol, m. 177-80° (EtOAc). Complete absence of elimination products in the deamination of 17β-amino steroids may reflect the presence of the angular Me group on the adjacent bridgehead C atom and suggests that a diazonium ion, rather than a carbonium ion, is the important intermediate.

IT Steroids
(Walden inversion and)

IT Walden inversion
(in steroids)

IT Deamination
(of A-nor-, B-nor- and 17-aminosteroids)

IT 521-17-5, Androst-5-ene-3β,17β-diol 1178-00-3, 2,3-Seco-5α-cholestane-2,3-dioic acid 1178-00-3, 1H-Benz[e]indene-6,7-diacetic acid, 3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl- 2310-36-3, A-Nor-5α-cholestan-2-one 2311-96-8, A-Nor-5α-cholestan-2α-ol 2493-92-7, A-Nor-5α-cholestan-2α-ol, acetate 4350-66-7, Androst-5-en-3β-ol, 17β- amino- 4350-67-8, Androst-5-en-3β-ol, 17β-acetamido-, acetate 6908-01-6, A-Nor-5β-cholestan-3-one 14772-37-3, A-Nor-5α-cholestan-2β-ol 14772-59-9, A-Nor-5α-cholestan-2β-ol, acetate 20853-64-9, 5α- Androstane, 17β-acetamido- 28097-22-5, 4-Indancarboxylic acid, 5-(2-carboxy-1-methyl-4-oxocyclohexyl)-1-(1,5-dimethylhexyl)hexahydro-7a-methyl- 29599-03-9, 4-Indancarboxylic acid, 5-(2-carboxy-1-methylcyclohexyl)-1-(1,5-dimethylhexyl)hexahydro-7a-methyl- 31239-17-5, 5α- Androstan-17β-amine 35878-83-2, A-Norcholest-3(5)-ene 56997-89-8, A-Norcholest-5-en-3-one 70182-75-1, A-Nor-5α-cholestan-2-one, oxime 85198-44-3, A-Nor-5β-cholestan-3β-ol 103366-02-5, B-Nor-5β,8α-cholestan-6-one 110346-39-9, 6,7-Seco-5α-cholestane-6,7-dioic acid, 3-oxo- 119677-75-7, B-Nor-8α-cholest-5-ene 122386-63-4, A-Nor-5α-cholestane, 2β-acetamido- 122386-64-5, A-Nor-5β-cholestane, 3α-acetamido- 122386-65-6, A-Nor-5β-cholestane, 3β-acetamido- 122386-75-8, A-Nor-5α-cholest-1-ene 122386-76-9, A-Nor-5α-cholest-2-ene 122386-85-0, B-Nor-5β,8α-cholestane, 6α-acetamido- 122386-90-7, B-Nor-5β,8α-cholestan-6-one, oxime 122441-37-6, A-Nor-5β-cholestan-3-one, oxime 122441-42-3, B-Nor-5β,8α-cholestan-6α-ol 122564-84-5, 6,7-Seco-5α-cholestane-6,7-dioic acid 122626-62-4, B-Nor-5β,8α-cholestan-6α-amine 122650-16-2, A-Nor-5α-cholestan-2β-amine 122650-17-3, A-Nor-5β-cholestan-3α-amine 122650-18-4, A-Nor-5β-cholestan-3β-amine
(preparation of)

IT 217-04-9, Dicyclopenta[a,f]naphthalene 240-05-1, Cyclopenta[a]fluorene (steroid derivs.)

L26 ANSWER 13 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:53586 CAPLUS
DOCUMENT NUMBER: 56:53586
ORIGINAL REFERENCE NO.: 56:10209a-i,10210a-e
TITLE: Halogenations with quaternary ammonium perhalides in a tetrahydrofuran. I. Choice of a reactant, bromination of cyclic ketals
AUTHOR(S): Marquet, Andree; Dvolaitzky, Maya; Kagan, Henri B.; Mamlok, Lonka; Ouannes, Catherine; Jaques, Jean
CORPORATE SOURCE: College of France, Paris
SOURCE: Bulletin de la Societe Chimique de France (1961) 1822-31
CODEN: BSCFAS; ISSN: 0037-8968
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OTHER SOURCE(S): CASREACT 56:53586

AB [Me3PhN]Br.Br2 (I) was a stable and readily accessible brominating agent which brominated dioxolanes in tetrahydrofuran to bromo derivs., which upon hydrolysis furnished the corresponding α-brominated ketones. This reaction was applied to a series of steroids. Me2NPh (21 cc.) in 40 cc. C6H6 treated with 16 cc. Me2SO4 and cooled gave [Me3PhN]MeSO4; a 10-g. portion in 40 cc. 24% HBr treated with 3 cc. Br gave 80% I containing 42.12.5% active Br. The tetrahydrofuran used in all bromination reactions was dried by treating 2-3 weeks with K, refluxing 15 hrs., and distilling The appropriate ketone (1 g.) in 50 cc. C6H6 treated with 1.5 g. (CH2OH)2, 30 mg. pMeC6H4SO3H (II), and the mixture refluxed through Na2SO4 gave the corresponding dioxolane; method A. The appropriate ketone (1 g.), 1 cc. (CH2OH)2, 2 cc. HC(OEt)3, and 60 mg. II refluxed 15 min. to 1 hr., neutralized with aqueous NaHCO3, and filtered gave the corresponding dioxolane; method B. By these methods were prepared the following compds. (m.p., [α]D, % yield, reaction time in min., and method given):2-methyl-2-phenyldioxolane (III), 59.60°, -, 65, 300, A; 17,17-ethylenedioxy-3β- hydroxy-5α androstane (IV), 152-4° (85% aqueous MeOH), -18°, 960, 88, A; acetate (V) of IV, 150.5-1.5° (MeOH), -25°, 73, 15, B (also obtained in 100% yield by acetylation of IV); 3,3- ethylenedioxy-5α-androstane (VI), 116-17° (EtOH), 0°, 95, 90, A; 17β-OH derivative (VII) of VI, 137-40° (MeOH), 7°, 90, 90, A [which acetylated gave the acetate (VIII), m.143-4°]; 7,7-ethylenedioxy-3β,17β-dipropionoxy-5α-androstane (IX), 142-5° (MeOH), -5°, 60, 60, A; 20,20-ethylenedioxy-3β-acetoxy-5α-pregnane (X), 171-3° (MeOH), -5°, 53, 240°, A (67% during 2.5 hrs. by method B). The appropriate dioxolane (1 g.) in 10 cc. tetrahydrofuran treated with the equivalent amount of I, poured into 5% aqueous NaHCO3, and filtered gave the following compds. (m.p., [α]D, and % yield given):2-bromomethyl-2-phenyldioxolane (XI), 59.5.61.5° (aqueous MeOH), -, 76; 16α-Br derivative (XII) of 17,17-ethylenedioxy-5α- androstane (XIII), 146-8° (EtOH), -48°, 56; 16α-Br derivative (XIV) of IV, 196.5-7.5° (MeOH), -48°, 63; 16α-Br derivative of V, 169.5-70° (MeOH), -42°, 44; 2α-Br derivative of VI, 158-60° (EtOH), 8°, 42 (purified with Girard P reagent); 2α-Br derivative of VIII, 216-21° (MeOH), 23°, 49; 6β-Br derivative of IX, 140-1.5° (MeOH), -20°, 30; 21-Br derivative of X, 173.5-74° (MeOH), 2°, 53. The appropriate brominated dioxolane (100 mg.), 4 cc. AcOH, 1 cc. H2O, and 0.1 cc. H2SO4 refluxed 15 min., cooled, diluted with H2O, and filtered gave the corresponding ketone; method C. The appropriate brominated dioxolane (100 mg.) in 10 cc. AcOH containing 0.5 cc. H2O and 0.1 cc. H2SO4 diluted with H2O

after the rotation did not change any longer and filtered or extracted with Et2O gave the corresponding ketone; method D. By these methods were prepared the following compds. (m.p., [α]D, and method given): 16α-bromo-17-oxo-5α- androstane (XV), 195-8° (EtOH), 52°, D; 3β-OH derivative (XVI) of XV, 160-2.5° (aqueous MeOH), 49, D; acetate of XVI, 173-4° (EtOH), 38, D; 2α-bromo-3-oxo-5α- androstane (XVII), 212-14° (decomposition) (EtOH), 30, D; 17β-AcO derivative of XVII, 177° (aqueous MeOH), 30°, C; 6β-bromo-3β,17β-dipropionoxy-7-oxo-5α- androstane (XVIII), 154-5° (MeOH), 21°, C; 21-bromo-3β-acetoxy-20-oxo-5α-pregnane (XIX), 141-3° (aqueous dioxane), 78°, C. The dioxolane of XVI hydrolyzed hot gave the acetate of XVI; a 250-mg. portion of crude hydrolysis product in 5 cc. MeOH refluxed 1 hr. with 0.3 cc. concd, HCl, diluted with H2O, and filtered gave XVI, m.1602° (MeOH). III (240 mg.) in 2 cc. CCl4 treated with 4 cc. Br-CCl4 (58.6 mg./cc.), diluted with 10% aqueous Na2CO3, and extracted with Et2O gave 192 mg. XI, m. 54.5-5.5°, m. 59.561.5° (aqueous MeOH), also obtained by ketalization of BzCH2Br. IV (4 g.) in 40 cc. C5H5N added to 4 g. CrO3 in 40 cc. C5H5N, the mixture kept overnight, diluted with 20 cc. isoPrOH, treated with 3 g. Celite 535, filtered, the residue washed with 50 cc. dioxane, and the combined filtrates diluted with H2O precipitated 3.2 g. 3-oxo derivative (XX) of IV, m. 195-6° (MeOCH2CH2OH), [α]D-3°. XX (5 g.), 7.5 g. NaOH, 12.5 cc. N2H4.H2O, and 75 cc. (HOCH2CH2)2O refluxed 2 hrs., heated 5 hrs. at 195-200°, poured into H2O, and filtered yielded 4.65 g. (crude) XIII, m. 145-6° (EtOAc), [α]D -23°. Me3COK from 2.3 g. K in 75 cc. dry xylene refluxed 16 hrs. with 2.9 g. XIV in 150 cc. dry xylene, diluted with iced H2O, and extracted with Et2O yielded 1.36 g. 3β-hydroxy17,17-ethylenedioxy-5α- androst-15-ene, m. 152-3° (MeOH),[α]D -85°. XII (210 mg.), 19 cc. AcOH, and 2 cc. H2O refluxed 2 hrs., treated with 500 mg. Zn dust, refluxed again 2 hrs., filtered, and diluted with H2O yielded 120 mg. 17-oxo5α-androstane, m. 117-19°, [α]D 87°. 3β,17β-Dipropionoxy-7-oxo-5α- androstane (580 mg.) in 8 cc. AcOH treated with 340 mg. Br in 4 cc. AcOH, diluted after 2 days with H2O, and extracted with Et2O gave 420 mg. 6-Br derivative (XXI), m. 182-3.5° (EtOH). XVIII (102 mg.) and 1,5 cc. 20% HBr-EtCO2H kept overnight and diluted with H2O yielded 87 mg. (crude) XXI, m. 175-7° (MeOH), [α]D -6°. 3β-Acetoxy-21-bromo-20-oxo-5α-pregnane (245 mg.) in 3.5 cc. HCONMe2 and 130 mg. NaOAc heated 2 hrs. under a stream of N at 60° and diluted with H2O yielded 218 mg. (crude) 3β,21-diacetoxy-20-oxo-5α-pregnane, m. 14850° (MeOH), [α]D 68°. 17βBenzoxy-3-oxo-5α-pregnane (XXII) (500 mg.) in 5 cc. MeOH stirred 1 hr. with 10 mg. II, kept overnight, treated with 5% aqueous NaHCO3, and filtered yielded 537 mg. (crude) 17β-benzoxy-3,3-dimethoxy-5α- androstane (XXIII), m. 153-4° (MeOH), [α]D 51°. XXII (800 mg.) in 10 cc. tetrahydrofuran and 700 mg. I gave in the usual manner 1 g. 2α-bromo-17β-benzoxy-3-oxo-5α- androstane (XXIV), m. 217° (MeOCH2CH2OH), [α]D 92° XXIII (500 mg.) in 5 cc. tetrahydrofuran with 430 mg. I gave 542 mg. (crude) XXII, m. 208-12° (MeOCH2CH2OH); 218 mg. 2nd crop. Isoandrosterone acetate (5.6 g.), 10 cc. CH2(CH2OH)2, 10 cc. HC(OEt)3, and 400 mg. II refluxed 25 min., diluted with aqueous NaHCO3, and filtered yielded 2.28 g. 3β-acetoxy-17,17-propylenedioxy-5α-ostane (XXV), m. 172-4° (MeOH), [α]D-10°. XXV (750 mg.) in 8 cc. tetrahydrofuran treated with 720 mg. I during 135 min. and worked up in the usual manner gave 495 mg. 3β-acetoxy16-bromo-17,17-trimethylenedioxy-5-androstane (XXVI), m. 190-3° (decomposition) (EtOH), [α]D 36°. XXXVI (220 mg.),17 cc AcOH, 2 cc. CHCl3 1 cc. H2O, and 0.2 cc. concentrated H2SO4 kept cold 50 min., diluted with H2O, the CHCl3 removed in an air stream, and the residue filtered

gave 192 mg. 17-oxo analog of XXVI, m. 144-6° (MeOH), [α]D 94° (CHCl3).

IT Acetals
(cyclic, bromination of, with trimethylphenylammonium tribromide)

IT Bromination
(of cyclic acetals with trimethylphenylammonium tribromide)

IT Halogenation
(with quaternary ammonium trihalides)

IT 21306-56-9, Ethanaminium, 2-[(2,6-dimethylphenyl)amino]-N,N,N-triethyl-2-oxo-
(halogenation with)

IT 109-99-9, Furan, tetrahydro-
(halogenation with quaternary ammonium trihalides in)

IT 1434-07-7, 5α- Androstan-17-one, cyclic ethylene acetal 3674-77-9, 1,3-Dioxolane, 2-methyl-2-phenyl- 15807-49-5, 5α-Androstan-17-one, 3β- hydroxy-, cyclic ethylene acetal
(preparation and bromination of)

IT 963-74-6, 5α- Androstan-17-one 1046-35-1, 5α-Androstan-3-one, 17β- hydroxy-, cyclic ethylene acetal 1242-54-2, 5α- Androstan-17-one, 16β-bromo-3β- hydroxy-, acetate 1242-55-3, 5α-Androstan-17-one, 16α-bromo-3β- hydroxy-, acetate 1434-14-6, 5α- Androstan-3-one, cyclic ethylene acetal 3418-21-1, 1,3-Dioxolane, 2-(bromomethyl)-2-phenyl- 3674-78-0, 5α- Androstan-17-one, 3β- hydroxy-, cyclic ethylene acetal, acetate 4207-56-1, Ammonium, trimethylphenyl, tribromide 5987-29-1, 5α- Androstan-17-one, 16α-bromo- 6173-35-9, 5α- Androstan-3-one, 2α-bromo-17β- hydroxy-, acetate 13067-39-5, 5α- Androstan-17-one, 16α-bromo-, cyclic ethylene acetal 15807-55-3, 5α- Androstane-3,17-dione, cyclic 17-(ethylene acetal) 16375-22-7, 5α- Androstan-3-one, 17β- hydroxy-, cyclic ethylene acetal, acetate 24352-29-2, 5α- Androstan-3-one, 17β- hydroxy-, dimethyl acetal, benzoate 28507-02-0, 5α- Androstan-17-one, 16α-bromo-3β- hydroxy- 40129-02-0, 5α-Pregnan-20-one, 3β,21-dihydroxy-, diacetate 50364-57-3, 5α- Androstan-3-one, 2α-bromo- 50763-82-1, 5α- Androstan-17-one, 16α-bromo-3β-hydroxy-, cyclic ethylene acetal 50763-83-2, 5α-Androst-15-en-17-one, 3β- hydroxy-, cyclic ethylene acetal 75886-29-2, 5α-Pregnan-20-one, 21-bromo-3β-hydroxy-, acetate 77731-19-2, 5α- Androstan-17-one, 16α-bromo-3β- hydroxy-, cyclic ethylene acetal, acetate 88843-63-4, 5α- Androstan-3-one, 2α-bromo-, cyclic ethylene acetal 95952-11-7, 5α-Pregnan-20-one, 3β- hydroxy-, cyclic ethylene acetal, acetate 96192-10-8, 5α- Androstan-3-one, 2α-bromo-17β-hydroxy-, benzoate 96365-84-3, 5α- Androstan-3-one, 2α-bromo-17β- hydroxy-, cyclic ethylene acetal, acetate 96974-18-4, 5α- Androstan-7-one, 3β,17β-dihydroxy-, cyclic ethylene acetal, dipropionate 97082-90-1, 5α- Androstan-7-one, 6β-bromo-3β,17β-dihydroxy-, cyclic ethylene acetal, dipropionate 98424-18-1, 5α-Pregnan-20-one, 21-bromo-3β- hydroxy-, cyclic ethylene acetal, acetate 101202-39-5, 5α- Androstan-17-one, 3β- hydroxy-, cyclic trimethylene acetal , acetate 103004-86-0, 5α- Androstan-17-one, 16β-bromo-3β-hydroxy-, cyclic trimethylene acetal, acetate 886200-64-2, 5α- Androstan-7-one, 6β-bromo-3β,17β-dihydroxy-, dipropionate 886200-66-4, 5α- Androstan-7-one, 6α-bromo-3β,17β-dihydroxy-, dipropionate

(preparation of)
IT 186-85-6, Spiro[17H-cyclopenta[a]phenanthrene-17,2'-m-dioxane]
(steroid derivs.)

L26 ANSWER 14 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1967:95379 CAPLUS
DOCUMENT NUMBER: 66:95379
TITLE: Steroids and related natural products. XXXVI. Structural biochemistry. 4. 3β- Hydroxy -17β-(L-prolyl)aminoandrost-5-ene
AUTHOR(S): Pettit, George R.; Smith, Robert Lawrence; Das Gupta, Arun K.; Occolowitz, John L.
CORPORATE SOURCE: Univ. of Maine, Orono, ME, USA
SOURCE: Canadian Journal of Chemistry (1967), 45(5), 501-7
CODEN: CJCHAG; ISSN: 0008-4042
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB cf. CA 65, 20208f; 66, 76285e. The synthesis of the title compound I was studied in detail and the following combination of methods was found reliable and convenient. The oxime derivative Ib of ketone Ia was reduced with Na-EtOH to 3β- hydroxy-17β- amino- androst-5-ene. The configurational assignment for amine IIa was supported by the results of a comparison with the 17α-epimer and by a proton magnetic resonance study of both isomers. Selective reaction between amine IIa and carbobenzyloxy-L-proline was achieved with Woodward's reagent K. Of several procedures explored for removing the carbobenzyloxy protecting group from amide IIc, Pd-catalyzed hydrogenolysis proved quite satisfactory. Hydrogenolysis of carbamate IIb to yield prolyl amide I was realized without affecting the Δ5-olefin system. A mass spectral study of amine I and the corresponding 5α-derivative (III) confirmed the latter observation. A brief review of procedures for the synthesis of steroidal amines is also presented.
IT Mass spectra
(of 17β-(2-pyrrolidinecarboxamido)-5α- androst -3β-ol and 17β-(2-pyrrolidinecarboxamido) androst -5-en-3β-ol)
IT 2-Pyrrolidinecarboxamide, N-(3β- hydroxy-5α- androstan-17β-yl)-, L-
5α- Androstan-3β-ol, 17β-(L-2- pyrrolidinecarboxamido)-
RL: PRP (Properties)
(mass spectrum of)
IT 3065-10-9P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and mass spectrum of)
IT 2830-48-0P 3249-06-7P 4350-66-7P 13650-22-1P 13650-25-4P 13650-27-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

L26 ANSWER 15 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:483686 CAPLUS
DOCUMENT NUMBER: 57:83686
ORIGINAL REFERENCE NO.: 57:16766i,16767a-c
TITLE: Hypocholesterolemic compositions
INVENTOR(S): Thorp, Jeffrey M.
PATENT ASSIGNEE(S): Imperial Chemical Industries Ltd.
SOURCE: 10 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 898596		19620614	GB 1960-8494	19600310
US 3097139		19630709	US 1961-92768	19610302

AB The mixts. containing salts or esters of α-(4-chlorophenoxy)isobutyric acid (I) and derivs. of androstane possess greater hypocholesterolemic activity than the derivs. of I alone, and as such suitable pharmaceutical compns. are prepared for oral use. The Na, K, or Ca salt, and Me, Et, or Pr ester of I, or of the related acid, α-(4-ethylphenoxy)isobutyric acid, are preferred for the purpose. The derivs. of androstane used in the compns. include androsterone (II), II acetate, II propionate, testosterone, 17α-hydroxyandrost-4-en-3-one, androstane -3α,17β-diol, 17β- hydroxy-19-norandrost-4-en-3-one, 17β- hydroxy-2-hydroxymethylene-17α-methylandrostan-3-one, androst-4-ene-3,17-dione, and 3β-hydroxyandrostan-17-one. The relative proportions of the androstane derivs. to the derivs. of I, used in the pharmaceutical formulations, such as capsules, tablets, sirups, suspensions, and emulsions, vary from 1:5 to 1:40. A preferred composition was prepared by mixing 200 parts of Et ester of I and 6 parts of androsterone and filling it into gelatin capsules, which are recommended for use with a daily rate of administration of 1-2 g. of the ester of I and 30-60 mg. of androsterone. The compns. may contain in addition an estrogen, such as estradiol, ethynylestradiol, hexestrol, or stilbestrol in a proportion so that oral administration of the compns. for therapeutic purposes provides a daily dose of estrogen within the range of 0.1-5.0 mg. Some prepns. containing vitamins, salts of glycerophosphoric acid, amino acids, proteins, and carbohydrates, in addition to the active ingredients, are also formulated. Cf. Brit. 860,303 (CA 55, 24680b).

IT Propionic acid, 2-(p-chlorophenoxy)-2-methyl-, calcium salt
(cholesterol-lowering preparation containing)

IT 50-28-2, Estradiol 53-41-8, Androsterone 57-63-6, 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol 58-18-4, Androst-4-en-3-one, 17β- hydroxy-17-methyl- 58-22-0, Testosterone 63-05-8, Androst -4-ene-3,17-dione 434-22-0, Estr-4-en-3-one, 17β- hydroxy- 481-30-1, Androst-4-en-3-one, 17α- hydroxy- 637-07-0, Propionic acid, 2-(p-chlorophenoxy)-2-methyl-, ethyl ester 1164-95-0, Androsterone, acetate 1852-53-5, Androstane-3α,17β-diol 5635-50-7, Phenol, 4,4'-(1,2-diethylethylene)di- 5953-68-4, Androsterone, propionate 6898-97-1, 4,4'-Stilbenediol, α,α'-diethyl- 17413-77-3, Propionic acid, 2-(p-ethylphenoxy)-2-methyl- 18045-52-8, Androstan-3-one, 17β- hydroxy-2-(hydroxymethylene)- 17-methyl- 20120-08-5, Androstan-17-one, 3β- hydroxy- 26723-02-4, Propionic acid, 2-(p-chlorophenoxy)-2-methyl-, potassium salt 55162-41-9, Propionic acid, 2-(p-chlorophenoxy)-2-methyl-, methyl ester 56532-11-7, Propionic acid, 2-(p-chlorophenoxy)-2-methyl-, propyl ester
(cholesterol-lowering preparation containing)

IT 57-88-5, Cholesterol
(in blood, effect of α-(4-chlorophenoxy)isobutyric acid and androstane derivs. on)

L26 ANSWER 16 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:520238 CAPLUS
DOCUMENT NUMBER: 137:214684
TITLE: Broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer

AUTHOR(S): Steketee, Karine; Timmerman, Leon; Ziel-Van der Made, Angelique C. J.; Doesburg, Paul; Brinkmann, Albert O.; Trapman, Jan
CORPORATE SOURCE: Department of Pathology, Josephine Nefkens Institute, Erasmus University, Rotterdam, 3000 DR, Neth.
SOURCE: International Journal of Cancer (2002), 100(3), 309-317
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a subset of endocrine therapy-resistant prostate cancers, amino acid substitutions H874Y, T877A and T877S, which broaden ligand specificity of the ligand binding domain (LBD) of the androgen receptor (AR), have been detected. To increase our knowledge of the role of amino acid substitutions at these specific positions in prostate cancer, codons 874 and 877 were subjected to random mutagenesis. AR mutants were screened in a yeast readout system for responsiveness to 5α-dihydrotestosterone, progesterone and dehydroepiandrosterone. At position 874, only the histidine to tyrosine substitution could broaden AR ligand specificity. At position 877, 4 ligand specificity broadening substitutions were found: T877A, T877S, T877C and T877G. The latter 2 were not found in prostate cancer. The AR mutants were tested in mammalian (Hep3B) cells for responsiveness to 13 different ligands. All mutants displayed their own ligand specificity spectrum. Importantly, AR(H874Y) and AR(T877A) could be activated by cortisol. According to the 3-dimensional structure of the AR LBD, T877 interacts directly with the 17β-hydroxyl group of androgens. All amino acid substitutions identified at position 877 had smaller side chains than the threonine in the wild-type receptor, indicating that increased space in the ligand binding pocket is important in broadened ligand specificity. Because H874 does not interact directly with the ligand, its substitution by a tyrosine is expected to change the ligand binding pocket conformation indirectly. For T877C and T877G substitutions, 2-point mutations are required, and for H874Y, T877A and T877S substitutions, only a 1-point mutation is sufficient. This most likely explains that the latter 3 have been found in prostate cancer.
IT Gene, animal
RL: PRP (Properties)
(AR; broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer)
IT Human
Prostate gland, neoplasm
(broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer)
IT Androgen receptors
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer)
IT Protein motifs
(ligand-binding domain; broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer)
IT Transcriptional regulation
(transcriptional activation, of gene AR; broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer)
IT 50-02-2, Dexamethasone 50-23-7, Cortisol 50-28-2, Estradiol,

biological studies 52-39-1, Aldosterone 53-43-0, Dehydroepiandrosterone 57-83-0, Progesterone, biological studies 63-05-8, Androstenedione 76-25-5, Triamcinolone acetonide 427-51-0, Cyproterone acetate 521-18-6, 5α-Dihydrotestosterone 965-93-5, R 1881 52806-53-8, Hydroxy -flutamide
RL: BSU (Biological study, unclassified); BIOL (Biological study) (broadened ligand responsiveness of androgen receptor mutants obtained by random amino acid substitution of H874 and mutation hot spot T877 in prostate cancer)
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 17 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1955:41883 CAPLUS
DOCUMENT NUMBER: 49:41883
ORIGINAL REFERENCE NO.: 49:7981a-e
TITLE: Steroid metabolism. XXI. The infrared spectra of keto steroids below 1350 cm.-1
AUTHOR(S): Jones, R. Norman; Herling, F.; Katzenellenbogen, E.
CORPORATE SOURCE: Natl. Research Council Can., Ottawa
SOURCE: Journal of the American Chemical Society (1955), 77, 651-61
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C.A. 48, 841c. The IR spectra of oxosteroids (I) show several distinguishable bands between 1350 and 650 cm.-1, the position of which serves to characterize the location of the oxo group and its relation to neighboring centers of unsatn. Many of these bands also can be recognized in the spectra of the diketones, keto-esters, and keto alcs. unless submerged beneath more intense absorption associated with the other functional substituents. Some of these characteristic frequencies may be perturbed by substitution in ring C. The characteristic absorption maximum of a series of 72 oxo steroids are tabulated. The IR absorption spectra are recorded for 3-etiocholanone, 3-androstanone, 1-androsten-17β-ol-3-one, 4- androsten-3-one, 1,4-cholestadien-3-one, 4,6-cholestadien-3-one, 5-cholesten-3β-ol-7-one acetate, 17-etiocholanone, 17-androstanone, pregnan-3α-ol-20-one, allopregnan 3β-ol-20-one, 4-androstene-3,17-dione, 3,20-pregnane dione, 1,4-androstadien-3, 17-dione, 1,4-androstadien -17β-ol-3-one, 1,4- androstadien-17β-ol-3-one hexahydrobenzoate, Me 3-oxo-1, 4-etiocholadienate.
IT Steroids
(metabolism of)
IT Metabolism, animal
(of steroids)
IT Spectra
(of steroids (keto))
IT 5-Pregnene-20-carboxylic acid, 3-hydroxy-7-oxo-, methyl ester acetate
7-Etioallocholenic acid, 3-oxo-, methyl ester
Pregnadiene-3,20-dione
(spectrum of)
IT 58-22-0, Testosterone
(and esters, spectra of)
IT 98-89-5, Cyclohexanecarboxylic acid
(esters, with steroids, spectra of)
IT 1201-56-5, Norephedrine, N,N-dimethyl-, DL-threo-
(spectra)
IT 53-41-8, Androsterone 53-42-9, 17-Etiocholanone, 3α-hydroxy- 516-55-2, 20-Allopregnanone, 3β- hydroxy-

571-31-3, 17-Etiocholanone, 3β- hydroxy- 846-48-0, 1,4-Androstadien-3-one, 17β- hydroxy- 853-23-6, 5-Androsten-17-one, 3β- hydroxy-, acetate 906-83-2, 20-Allopregnanone, 3β- hydroxy-, acetate 1164-95-0, Androsterone, acetate 1239-31-2, 17-Androstanone, 3β- hydroxy-, acetate 1482-78-6, Etiocholanone, 3α- hydroxy-, acetate 4820-41-1, 17-Etiocholanone, 3β- hydroxy-, acetate 5692-03-5, 3-Etiocholanone, 17α- hydroxy- 20120-08-5, 17-Androstanone, 3β- hydroxy- 39845-99-3, 20-Pregnanone, 3α- hydroxy- 62560-55-8, Norephedrine, N,N-dimethyl-, DL-erythro- 65556-92-5, 20-Pregnanone, 3α- hydroxy-, acetate 66905-19-9, 1,4-Androstadien-3-one, 17β- hydroxy-, cyclohexanecarboxylate 95119-07-6, 3-Etiocholanone, 17α- hydroxy-, acetate
(spectra of)

IT 4380-72-7, Benzamide, N-(β- hydroxy-α-methylphenethyl)- N-methyl- 54852-85-6, Ethanol, 2-methylamino-1,2-diphenyl-
(spectra of DL-erythro- and DL-threo-)

IT 57-83-0, Progesterone 63-05-8, 4-Androstene-3,17-dione 128-23-4, 3,20-Pregnanedione 566-65-4, 3,20-Allopregnanedione 566-91-6, 1,4-Cholestadien-3-one 566-93-8, 4,6-Cholestadien-3-one 601-57-0, 4-Cholesten-3-one 633-34-1, 4,6-Androstadiene -3,17-dione 809-51-8, 5-Cholesten-7-one, 3β- hydroxy-, acetate 848-62-4, 20-Allopregnanone 897-06-3, 1,4-Androstadiene-3,17-dione 969-72-2, 2-Allopregnen-20-one 1162-56-7, 4,6-Pregnadiene-3,20-dione 1229-12-5, 3,17-Etiocholanedione 1235-98-9, Testosterone, 17-vinyl- 1449-61-2, 5-Androstene -7,17-dione, 3β- hydroxy-, acetate 1778-02-5, 5-Pregnen-20-one, 3β- hydroxy-, acetate 1912-61-4, 17-Etiocholanone 2872-90-4, 4-Androsten-3-one 5982-99-0, 3,17-Androstanedione 6618-29-7, 9(11)-Allopregnen-20-one, 3β- hydroxy-, acetate 14639-79-3, 2-Androsten -17-one 14778-11-1, 3-Allopregnanone 15600-08-5, 3-Cholestanone 18069-68-6, 3-Etiocholanone 21507-41-5, 1-Androstene -3,17-dione 23498-50-2, 3-Coprostanone, oxime 29873-50-5, 3-Androstanone, 17β- hydroxy- 35290-68-7, 1-Androsten-3-one, 17β- hydroxy- 36378-49-1, 17-Androstanone 50557-39-6, 1-Cholesten-3-one 65635-48-5, 3-Androstanone 95564-19-5, 1-Allopregnene-3,20-dione, 21-hydroxy-, acetate 96946-79-1, 3,20-Pregnanedione, 21-hydroxy-, acetate 106760-08-1, 20-Pregnanone, 3β- hydroxy-, acetate 111497-46-2, 1,4-Androstadiene -17β-carboxylic acid, 3-oxo-, methyl ester 882743-69-3, 1-Androsten-3-one, 17β- hydroxy-, cyclohexanecarboxylate
(spectrum of)

IT 42551-55-3, 2-Butanol, 3-amino-
(spectrum of DL-erythro-)

L26 ANSWER 18 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:284134 CAPLUS
DOCUMENT NUMBER: 142:349472
TITLE: As-needed administration of an androgenic agent to enhance female desire and responsiveness
INVENTOR(S): Wilson, Leland F.; Tam, Peter Y.
PATENT ASSIGNEE(S): Vivus Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U.S. Ser. No. 919,472.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005070516	A1	20050331	US 2004-990667	20041116
US 5877216	A	19990302	US 1997-959064	19971028
US 6306841	B1	20011023	US 2000-539484	20000330
US 2002013304	A1	20020131	US 2001-919472	20010727
PRIORITY APPLN. INFO.:			US 1997-959057 B2	19971028
			US 1997-959064 A2	19971028
			US 1998-181316 B1	19981027
			US 2000-539484 A2	20000330
			US 2001-919472 A2	20010727

AB A method is provided for enhancing a female individual's sexual desire and responsiveness. The method involves administration of a pharmaceutical formulation containing an effective amount of an androgenic agent, wherein administration is on an as-needed basis rather than involving chronic pharmacotherapy. Local delivery may be accomplished via administration to the vagina, vulvar area or urethra of the individual, although oral administration is preferred for those androgenic agents that are orally active. Formulations and kits for carrying out the method are provided as well.

IT Androgen receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SARMs as addnl. active agents; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Leukotriene antagonists
Muscle relaxants
Vasodilators
(as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Growth factors, animal
Prostaglandins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 5-HT agonists
5-HT antagonists
Calcium channel blockers
Dopamine agonists
Dopamine antagonists
Potassium channel blockers
Potassium channel openers
(as addnl. active agents; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Amino acids, biological studies
Neuropeptides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as addnl. active agents; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Combination chemotherapy
(as-needed administration of an androgenic agent in combination with another agent to enhance female desire and responsiveness)

IT Drug delivery systems
Human
Sexual behavior
(as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Androgens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Vagina, disease
(atrophy, method of preventing; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(buccal; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Reproductive system
(female, method of maintaining health of female genitalia; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(inhalants; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Vagina, disease
(itching and dryness, method of preventing; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(nasal; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Steroids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonandrogenic, as addnl. active agents; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(ointments, creams; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(ointments; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Vagina, disease
(pain during intercourse, method of preventing; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(parenterals; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidyl drugs as addnl. active agents; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(rectal; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(sublingual; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(suppositories, vaginal; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(sustained-release; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(transdermal; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(vaginal; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Cardiovascular agents

(vasoactive agent as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT Drug delivery systems
(vulvar region; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 37221-79-7, Vasoactive intestinal polypeptide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists, as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 116243-73-3D, Endothelin, peptides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists, as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 363-24-6, Dinoprostone 363-24-6D, PGE2, esters 551-11-1, PGF2α 551-11-1D, PGF2α, esters 745-62-0, PGF1α 745-62-0D, PGF1α, esters 745-64-2, PGF3α 745-64-2D, PGF3α, esters 745-65-3, PGE1 745-65-3D, PGE1, esters 802-31-3, PGE3 802-31-3D, PGE3, esters 3434-33-1 13345-46-5, 19-Hydroxy -PGB1 13345-46-5D, 19-Hydroxy-PGB1, esters 13345-50-1, PGA2 13345-50-1D, PGA2, esters 13345-51-2, PGB1 13345-51-2D, PGB1, esters 13367-85-6, PGB2 13367-85-6D, PGB2, esters 14152-28-4, PGA1 14152-28-4D, PGA1, esters 19313-28-1, PGE0 19313-28-1D, PGE0, esters 20592-60-3 23726-87-6 31753-17-0, PGE2 methyl ester 35121-78-9, PGI2 35121-78-9D, PGI2, esters 35700-27-7 35900-16-4, PGE1 ethyl ester 36614-32-1, PGB3 36614-32-1D, PGB3, esters 38562-01-5, Dinoprost tromethamine 39746-25-3, 16,16-Dimethyl-PGE2 41598-07-6, PGD2 41598-07-6D, PGD2, esters 41692-15-3 51924-48-2, PGE2 ethyl ester 51953-95-8 53658-98-3, 11-Deoxy-16,16-dimethyl-PGE2 55028-70-1, Arbaprostil 55123-67-6, 19-Hydroxy-PGE1 55123-67-6D, 19-Hydroxy-PGE1, esters 55123-68-7, 19-Hydroxy-PGE2 55123-68-7D, 19-Hydroxy-PGE2, esters 58551-69-2, Carboprost tromethamine 60325-46-4, Sulprostone 61263-35-2, Meteneprost 63266-93-3, 19(R)-Hydroxy-PGE2 64318-79-2, Gemeprost 67392-20-5, 19-Hydroxy-PGB2 67392-20-5D, 19-Hydroxy -PGB2, esters 69256-46-8, 19-Hydroxy-PGA2 69256-46-8D, 19-Hydroxy-PGA2, esters 69552-46-1, Carbaprostacyclin 69900-72-7, 11-Deoxy-11α,16,16-trimethyl-PGE2 71116-82-0, Tiaprost 71845-66-4 72079-25-5 73121-56-9, Enprostil 73647-73-1D, Viprostol, acid-w/o Me ester 78919-13-8, Iloprost 81445-69-4 90880-94-7, Endothelium-derived relaxant factor 91326-98-6, 19-Hydroxy -PGA1 91326-98-6D, 19-Hydroxy-PGA1, esters 93000-00-1 122576-55-0 128908-32-7D, Melanocortin, peptides 191532-28-2 217182-28-0 393588-32-4 848849-83-2 848849-84-3 848849-85-4 848849-86-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 58-00-4, Apomorphine 59-92-7, Levodopa, biological studies 3605-01-4, Piribedil 25614-03-3, Bromocriptine 66104-22-1, Pergolide 91374-21-9, Ropinirole 104632-26-0, Pramipexole
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as addnl. active agents; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 53-39-4, Oxandrolone 53-39-4D, Oxandrolone, salts and esters 53-41-8, Androsterone 53-41-8D, Androsterone, salts and esters 53-43-0, Dehydroepiandrosterone 53-43-0D, Dehydroepiandrosterone, salts and esters 57-85-2, Testosterone propionate 58-18-4, Methyl testosterone 58-18-4D, Methyl testosterone, salts and esters 58-19-5, Dromostanolone 58-19-5D, Dromostanolone, salts and esters 58-20-8, Testosterone cypionate 58-22-0, Testosterone 58-22-0D, Testosterone, salts and esters 63-05-8, Androstenedione

63-05-8D, Androstenedione, salts and esters 76-43-7, Fluoxymesterone 76-43-7D, Fluoxymesterone, salts and esters 315-37-7, Testosterone heptanoate 434-07-1, Oxymetholone 434-07-1D, Oxymetholone, salts and esters 434-22-0, Nandrolone 434-22-0D, Nandrolone, salts and esters 521-17-5, Androstenediol 521-17-5D, Androstenediol, salts and esters 521-18-6, 4-Dihydrotestosterone 521-18-6D, 4-Dihydrotestosterone, salts and esters 965-90-2, Ethylestrenol 965-90-2D, Ethylestrenol, salts and esters 968-93-4, Testolactone 968-93-4D, Testolactone, salts and esters 5704-03-0, Testosterone phenyl acetate 5721-91-5, Testosterone caprate 5949-44-0, Testosterone undecanoate 10418-03-8, Stanazolol 10418-03-8D, Stanazolol, salts and esters 57361-80-5, Testosterone isocaprate 105165-22-8, Testosterone buciclate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as-needed administration of an androgenic agent to enhance female desire and responsiveness)

IT 182372-13-0, Rho kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, as addnl. active agent; as-needed administration of an androgenic agent to enhance female desire and responsiveness)

L26 ANSWER 19 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:90612 CAPLUS
DOCUMENT NUMBER: 136:145563
TITLE: As-needed administration of an androgenic agent to enhance female sexual desire and responsiveness
INVENTOR(S): Wilson, Leland F.; Tam, Peter Y.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U.S. 6,306,841.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002013304	A1	20020131	US 2001-919472	20010727
US 5877216	A	19990302	US 1997-959064	19971028
US 6306841	B1	20011023	US 2000-539484	20000330
CA 2455728	AA	20030213	CA 2002-2455728	20020726
WO 2003011301	A1	20030213	WO 2002-US23847	20020726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1420795	A1	20040526	EP 2002-753419	20020726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005503374	T2	20050203	JP 2003-516531	20020726
US 2005070516	A1	20050331	US 2004-990667	20041116

PRIORITY APPLN. INFO.:

US 1997-959057	B2 19971028
US 1997-959064	A2 19971028
US 1998-181316	B1 19981027
US 2000-539484	A2 20000330

US 2001-919472 A 20010727
WO 2002-US23847 W 20020726

AB A method is provided for enhancing a female individual's sexual desire and responsiveness. The method involves administration of a pharmaceutical formulation containing an effective amount of an androgenic agent, wherein administration is on an as-needed basis rather than involving chronic pharmacotherapy. Local delivery may be accomplished via administration to the vagina, vulvar area or urethra of the individual, although oral administration is preferred for those androgenic agents that are orally active. Formulations and kits for carrying out the method are provided as well. The androgenic agents can be used in combination with at least one addnl. active agent, such as a vasodilator.

IT Androgen receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SARMs (selective androgen receptor modulators); as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Urethra
(administration site; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Vagina
(administration site; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT 5-HT agonists
5-HT antagonists
Calcium channel blockers
Cardiovascular agents
Dopamine agonists
Dopamine antagonists
Potassium channel blockers
Potassium channel openers
Vasodilators
(as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Amino acids, biological studies
Growth factors, animal
Neuropeptides
Prostaglandins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(buccal; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drugs; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Blood vessel
(endothelium, -derived relaxation factors; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Human
Sexual behavior
(formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Androgens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(inhalants; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Leukotrienes
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(intranasal; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Steroids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonandrogenic; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(ointments, creams; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(ointments; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(parenterals; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Drugs
(peptidyl; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Vagina
(prevention of vaginal atrophy, itching, and dryness; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(rectal; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Muscle relaxants
(smooth; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(sublingual; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(suppositories, vaginal; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(tablets; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(topical; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Drug delivery systems
(transdermal; formulations containing androgenic agents for as-needed

administration to enhance female sexual desire and responsiveness)

IT Endothelium
(vascular, -derived relaxation factors; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT Reproductive system
(vulva, administration site; formulations containing androgenic agents for as-needed administration to enhance female sexual desire and responsiveness)

IT 37221-79-7, Vasoactive intestinal polypeptide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT 116243-73-3, Endothelin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT 363-24-6, Dinoprostone 363-24-6D, PGE2, esters 551-11-1, PGF2α 551-11-1D, PGF2α, esters 745-62-0, PGF1α 745-62-0D, PGF1α, esters 745-64-2, PGF3α 745-64-2D, PGF3α, esters 745-65-3, Lipoprost 745-65-3D, PGE1, esters 802-31-3, PGE3 802-31-3D, PGE3, esters 3434-33-1 13345-46-5, 19-Hydroxy -PGB1 13345-46-5D, 19-Hydroxy-PGB1, esters 13345-50-1, PGA2 13345-50-1D, PGA2, esters 13345-51-2, PGB1 13345-51-2D, PGB1, esters 13367-85-6, PGB2 13367-85-6D, PGB2, esters 14152-28-4, PGA1 14152-28-4D, PGA1, esters 19313-28-1, PGE0 19313-28-1D, PGE0, esters 20592-60-3 23726-87-6 31753-17-0, PGE2 methyl ester 35121-78-9, PGI2 35121-78-9D, PGI2, esters 35700-27-7 35900-16-4, PGE1 ethyl ester 36614-32-1, PGB3 36614-32-1D, PGB3, esters 38562-01-5, Dinoprost tromethamine 39746-25-3, 16,16-Dimethyl-PGE2 41598-07-6, PGD2 41598-07-6D, PGD2, esters 41692-15-3 51924-48-2, PGE2 ethyl ester 51953-95-8 53658-98-3, 11-Deoxy-16,16-dimethyl-PGE2 55028-70-1, Arbaprostil 55123-67-6, 19-Hydroxy-PGE1 55123-67-6D, 19-Hydroxy-PGE1, esters 55123-68-7, 19-Hydroxy-PGE2 55123-68-7D, 19-Hydroxy-PGE2, esters 58551-69-2, Carboprost tromethamine 59122-46-2 60325-46-4, Sulprostone 61263-35-2, Meteneprost 63266-93-3, 19(R)-Hydroxy-PGE2 64318-79-2, Gemeprost 67392-20-5, 19-Hydroxy-PGB2 67392-20-5D, 19-Hydroxy-PGB2, esters 69256-46-8, 19-Hydroxy-PGA2 69256-46-8D, 19-Hydroxy-PGA2, esters 69552-46-1, Carbaprostacyclin 69900-72-7, 11-Deoxy-11α,16,16-trimethyl-PGE2 71116-82-0, Tiaprost 71845-66-4 73121-56-9, Enprostil 73647-73-1, Viprostol 78919-13-8, Iloprost 91326-98-6, 19-Hydroxy-PGA1 91326-98-6D, 19-Hydroxy-PGA1, esters 128908-32-7D, Melanocortin, peptides 217182-28-0 223785-94-2 393588-32-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as-needed administration of androgenic agent in combination with other active agents to enhance female sexual desire and responsiveness)

IT 53-39-4, Oxandrolone 53-39-4D, Oxandrolone, esters and salts 53-41-8, Androsterone 53-41-8D, Androsterone, esters and salts 53-43-0, Dehydroepiandrosterone 53-43-0D, Dehydroepiandrosterone, esters and salts 57-85-2, Testosterone propionate 58-18-4, Methyl testosterone 58-18-4D, Methyl testosterone, esters and salts 58-19-5, Dromostanolone 58-19-5D, Dromostanolone, esters and salts 58-20-8, Testosterone cypionate 58-22-0, Testosterone 58-22-0D, Testosterone, esters and salts 63-05-8, Androstenedione 63-05-8D, Androstenedione, esters and salts 76-43-7, Fluoxymesterone 76-43-7D, Fluoxymesterone, esters and salts 315-37-7, Testosterone enanthate 434-07-1, Oxymetholone 434-07-1D, Oxymetholone, esters and salts 434-22-0, Nandrolone 434-22-0D, Nandrolone, esters

and salts 521-17-5, Androstenediol 521-17-5D
, Androstenediol, esters and salts 521-18-6,
4-Dihydrotestosterone 521-18-6D, 4-Dihydrotestosterone, esters and salts
965-90-2, Ethylestrenol 965-90-2D, Ethylestrenol, esters and salts
968-93-4, Testolactone 968-93-4D, Testolactone, esters and salts
1045-69-8, Testosterone acetate 5704-03-0, Testosterone phenylacetate
5721-91-5, Testosterone decanoate 5949-44-0, Testosterone undecanoate
10418-03-8, Stanozolol 10418-03-8D, Stanozolol, esters and salts
15262-86-9, Testosterone isocaproate 105165-22-8, Testosterone buciclate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(formulations containing androgenic agents for as-needed administration to
enhance female sexual desire and responsiveness)

IT 182372-13-0, Rho kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; as-needed administration of androgenic agent in
combination with other active agents to enhance female sexual desire
and responsiveness)

L26 ANSWER 20 OF 103 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:784893 CAPLUS
DOCUMENT NUMBER: 128:150926
TITLE: Expression and characterization of recombinant type 2 3α-hydroxysteroid dehydrogenase (HSD) from human prostate: demonstration of bifunctional 3α/17β-HSD activity and cellular distribution
AUTHOR(S): Lin, Hsueh-Kung; Jez, Joseph M.; Schlegel, Brian P.; Peehl, Donna M.; Pachter, Jonathan A.; Penning, Trevor M.
CORPORATE SOURCE: Dep. Pharmacol., Biochem., Biophys., Univ. Pennsylvania Sch. Med., Philadelphia, PA, 19104, USA
SOURCE: Molecular Endocrinology (1997), 11(13), 1971-1984
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In androgen target tissues, 3α-hydroxysteroid dehydrogenase (3α-HSD) may regulate occupancy of the androgen receptor (AR) by catalyzing the interconversion of 5α-dihydrotestosterone (5α-DHT) (a potent androgen) and 3α- androstanediol (a weak androgen). In this study, a 3α-HSD cDNA (1170 bp) was isolated from a human prostate cDNA library. The human prostatic 3α-HSD cDNA encodes a 323- amino acid protein with 69.9%, 84.1%, 99.4%, and 87.9% sequence identity to rat liver 3α-HSD and human type 1, type 2, and type 3 3α-HSDs, resp., and is a member of the aldo-keto reductase superfamily. The close homol. with human type 2 3α-HSD suggests that it is either identical to this enzyme or a structural allele. Surprisingly, when the recombinant protein was expressed and purified from Escherichia coli, the enzyme did not oxidize androsterone when measured spectrophotometrically, an activity previously assigned to recombinant type 2 3α-HSD using this assay. Complete kinetic characterization of the purified protein using spectrophotometric, fluorometric, and radiometric assays showed that the catalytic efficiency favored 3α- androstanediol oxidation over 5α-DHT reduction Using [14C]-5α-DHT as substrate, TLC anal. confirmed that the reaction product was [14C]-3α- androstanediol. However, in the reverse reaction, [3H]-3α- androstanediol was oxidized first to [3H]-androsterone and then to [3H]-androstanedione, revealing that the expressed protein possessed both 3α- and 17β-HSD activities. The 17β-HSD activity accounted for the higher catalytic efficiency observed with 3α- androstanediol. These findings indicate that, in

the prostate, type 2 3α-HSD does not interconvert 5α-DHT and 3α- androstanediol but inactivates 5α-DHT through its 3-ketosteroid reductase activity. Levels of 3α-HSD mRNA were measured in primary cultures of human prostatic cells and were higher in epithelial cells than stromal cells. In addition, elevated levels of 3α-HSD mRNA were observed in epithelial cells derived from benign prostatic hyperplasia and prostate carcinoma tissues. Expression of 3α-HSD was not prostate specific, since high levels of mRNA were also found in liver, small intestine, colon, lung, and kidney. This study is the first complete characterization of recombinant type 2 3α-HSD demonstrating dual activity and cellular distribution in the human prostate.

IT Prostate gland
(benign hyperplasia; cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT Enzyme kinetics
Michaelis constant
Prostate gland
Protein sequences
cDNA sequences
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT Androgens
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT Prostate gland
(carcinoma; cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 189049-63-6P
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(amino acid sequence; cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 9015-81-0P, 17β- Hydroxy steroid dehydrogenase 9028-56-2P, 3α-Hydroxysteroid dehydrogenase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional

3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 42616-29-5, 3-Ketosteroid reductase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 58-22-0, Testosterone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 1852-53-5
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 53-41-8, Androsterone 846-46-8
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 521-18-6, 5α-Dihydrotestosterone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inactivation; cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

IT 202538-42-9
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; cDNA cloning of human prostate type 2 3α-hydroxysteroid dehydrogenase, tissue distribution of mRNA, and bifunctional 3α/17β-hydroxysteroid dehydrogenase activity recombinant enzyme)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s 1991:549979/an
L27 1 1991:549979/AN

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L27 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:549979 CAPLUS
DOCUMENT NUMBER: 115:149979
TITLE: Induction of macrophage tumoricidal activity, major histocompatibility complex class II antigen (Iak) expression, and interleukin-1 production by swainsonine
AUTHOR(S): Grzegorzewski, Krzysztof; Newton, Sheila A.; Akiyama, Steven K.; Sharrow, Susan; Olden, Kenneth; White,

Sandra L.
CORPORATE SOURCE: Cancer Cent., Howard Univ., Washington, DC, 20060, USA
SOURCE: Cancer Communications (1989), 1(6), 373-9
CODEN: CNCMET; ISSN: 0955-3541
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies are presented to show that swainsonine was effective in activating peritoneal macrophages to cytotoxicity against tumor cells. Stimulation of tumoricidal activity of macrophages was associated with increased secretion of interleukin-1 (IL-1) and expression of the Iak major histocompatibility complex (MHC) antigen on the cell surface. The 3-fold stimulation of cytotoxicity observed in these in vivo studies was comparable to that obtained with Corynbacterium parvum, a commonly used in vivo activating agent. The in vitro incubation of thioglycollate-elicited peritoneal macrophages with swainsonine consistently resulted in levels of activation (6- to 8-fold) comparable to that obtained by treatment with known in vitro macrophage activating agents such as lipopolysaccharide (LPS) or recombinant gamma-interferon (rIFN-γ). The stimulation observed by using a swainsonine in combination with LPS was additive, suggesting different mechanisms of action. These studies have important implications not only for treatment of cancer, infectious diseases, and immune suppressive disorders, but also for elucidation of the mechanism of macrophage activation.

IT Immunostimulation
(from swainsonine, macrophage tumoricidal activity induction in)
IT Lipopolysaccharides
RL: BIOL (Biological study)
(macrophage tumoricidal activity stimulation by swainsonine enhancement by)
IT Neoplasm inhibitors
(swainsonine as, macrophage cytotoxicity stimulation in)
IT Macrophage
(cytotoxic, swainsonine induction of, tumoricidal activity in)
IT Antigens
RL: BIOL (Biological study)
(histocompatibility, class II, expression of, in macrophage tumoricidal activity, swainsonine effect on)
IT Lymphokines and Cytokines
RL: FORM (Formation, nonpreparative)
(interleukin 1, formation of, swainsonine effect on, macrophage tumoricidal activity induction in relation to)
IT 72741-87-8, Swainsonine
RL: BIOL (Biological study)
(macrophage tumoricidal activity stimulation by, mechanism of)

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(FILE 'HOME' ENTERED AT 15:42:25 ON 29 JUL 2006)

FILE 'REGISTRY' ENTERED AT 15:43:06 ON 29 JUL 2006
L1 0 S 3_-HYDROXY-5-ANDROSTENE-17_-METHYLAMINE
L2 0 S HYDROXY (L) ADROSTENE (L) METHYLAMINE
L3 0 S ADROSTENE (L) METHYLAMINE

FILE 'CAPLUS' ENTERED AT 15:44:43 ON 29 JUL 2006
L4 0 S 3_-HYDROXY-5-ANDROSTENE-17_-METHYLAMINE
S 177794-30-8/REG#

FILE 'REGISTRY' ENTERED AT 16:05:04 ON 29 JUL 2006
L5 1 S 177794-30-8/RN

FILE 'CAPLUS' ENTERED AT 16:05:04 ON 29 JUL 2006

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L6           10 S L5

     FILE 'REGISTRY' ENTERED AT 16:05:41 ON 29 JUL 2006
L7            1 S 177794-30-8

     FILE 'CAPLUS' ENTERED AT 16:06:39 ON 29 JUL 2006
L8            0 S 5 ANDROSTENE (L) METHYLAMINE
L9            2 S ANDROSTENE (L) METHYLAMINE
L10           0 S US2003651515/APPS
L11           1 S US2003-651515/APPS
                SELECT L11 1 RN
L12           4 S E50-151, E36-41
L13      530498 S E1-E162
L14        2344 S L13 AND (GRAFT OR GRAFT VERSUS HOST OR ORGAN REJECTION OR ORG
L15           0 S L4 AND (ANDROST? OR ANDROSTENE)
L16          19 S L14 AND (ANDROST? OR ANDROSTENE)

     FILE 'STNGUIDE' ENTERED AT 16:35:44 ON 29 JUL 2006
L17           0 S US2005101581/PN
L18           0 S US2005101581/APPS

     FILE 'CAPLUS' ENTERED AT 16:38:16 ON 29 JUL 2006
L19           0 S US2005101581/APPS
L20           1 S US2005-101581/APPS
L21       61816 S E1-E28, E33-34, E37-49
L22        4292 S L21 AND AMINO
L23         321 S L22 AND ANDROST?
L24         103 S L23 AND HYDROXY
L25           0 S L2 AND (IMMUNE? OR IMMUNO? OR TRANSPLANT? OR GRAFT? OR LIVER
L26         103 FOCUS L24 1-
L27           1 S 1991:549979/AN
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